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CASE REPORT

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

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Background: Situs inversus totalis (SIT) is a rare genetic congenital disease, characterized with complete right-to-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 markers (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.

Keywords: situs inversus totalis, gallbladder adenosquamous carcinoma

Background

Situs inversus totalis (SIT) is a rare genetic predisposition where 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 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 that patients with ciliary dyskinesia might present with obvious mobility dysfunction.[5] Therefore, SIT is found occasionally in routine imaging studies in most circumstances.

Due to the altered anatomical position of the vessels and organs in SIT, anatomical dissection and surgical resection proposed greater technical challenges to the surgeons.[6] So far, there have been several excellent cases of laparoscopic cholecystectomy in patients with SIT through advanced surgical techniques.[7] On the contrary, only a few cases of successful surgical treatments in SIT patients of esophageal cancer, pancreatic cancer, or ovarian cancer have been reported.[8–10] To our knowledge, report of SIT combined with gallbladder cancer has been rare. Here,

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we 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 scan found a mirror-image dextrocardia (Figure 1A), and further computed tomography (CT) revealed a complete, right-to-left reverse transposition of the organs in the thoracic cavity and the abdomen (Figure 1B and C), 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 (Figure 2A and B). 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 guideline.[11] Multiple vascular variations were also seen in addition to the right-to-left reversal anomaly (Figure 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. Polysplenia syndrome is defined as the existence of multiple, two to six, spleens similar in size, which are different from the accessory spleen.[12] Until now, it is not clear whether a relationship exists 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 colectomy 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 100 mL. Gross anatomy showed multiple gallstones in the gallbladder and a huge tumor at the gallbladder bottom, invading the transverse colon and the liver (Figure 3A and B). Final pathology revealed a moderately differentiated adenosquamous carcinoma of the gallbladder, invading the submucosa of the transverse colon (Figure 3C and D), further confirmed by immunohistochemical staining showing positive P63, P53, CK5/6, CK19, CK7, CK20, and CDX2, and negative ERBR expression (Figure 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 remains unclear, majorly caused by genetic mutations and chromosomal abnormalities.[3,13] As SIT itself does not seriously affect the function of organs, most patients will not have any abnormal feeling and it is mainly found during radiological examinations. However, the incidence of cardiovascular, hepatobiliary, and spleen malformations, accompanied with anomalies of abdominal vessels origination or distribution, markedly increases in SIT patients.[14,15] In our case, two major anatomical malformations were presented. One malformation was the vascular variation. In normal circumstances, the celiac trunk divides into the common hepatic artery, the splenic artery, and the left gastric artery. In this patient,

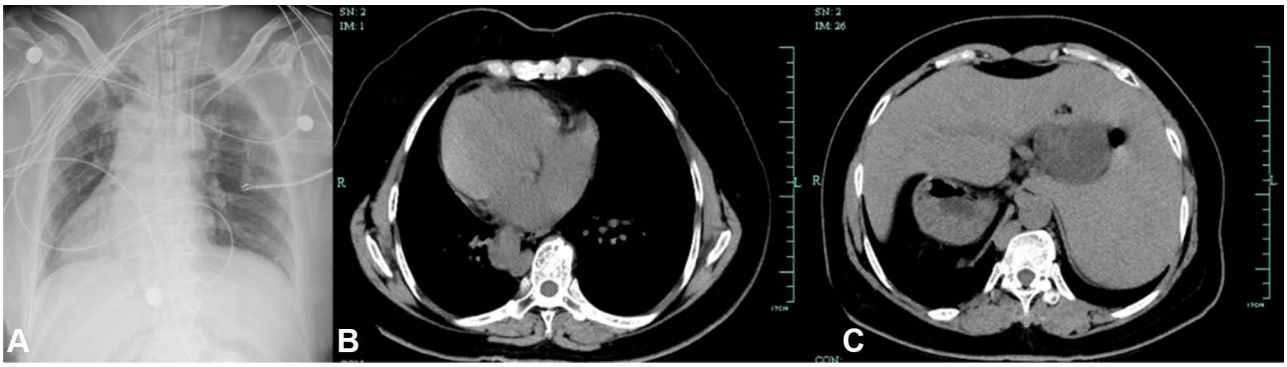

Figure 1 Radiology studies revealed SIT anomaly. (**A**) Dextrocardia in the chest X-ray image, right-to-left reverse transposition in (**B**) thoracic and (**C**) abdominal computed tomography (CT) images.

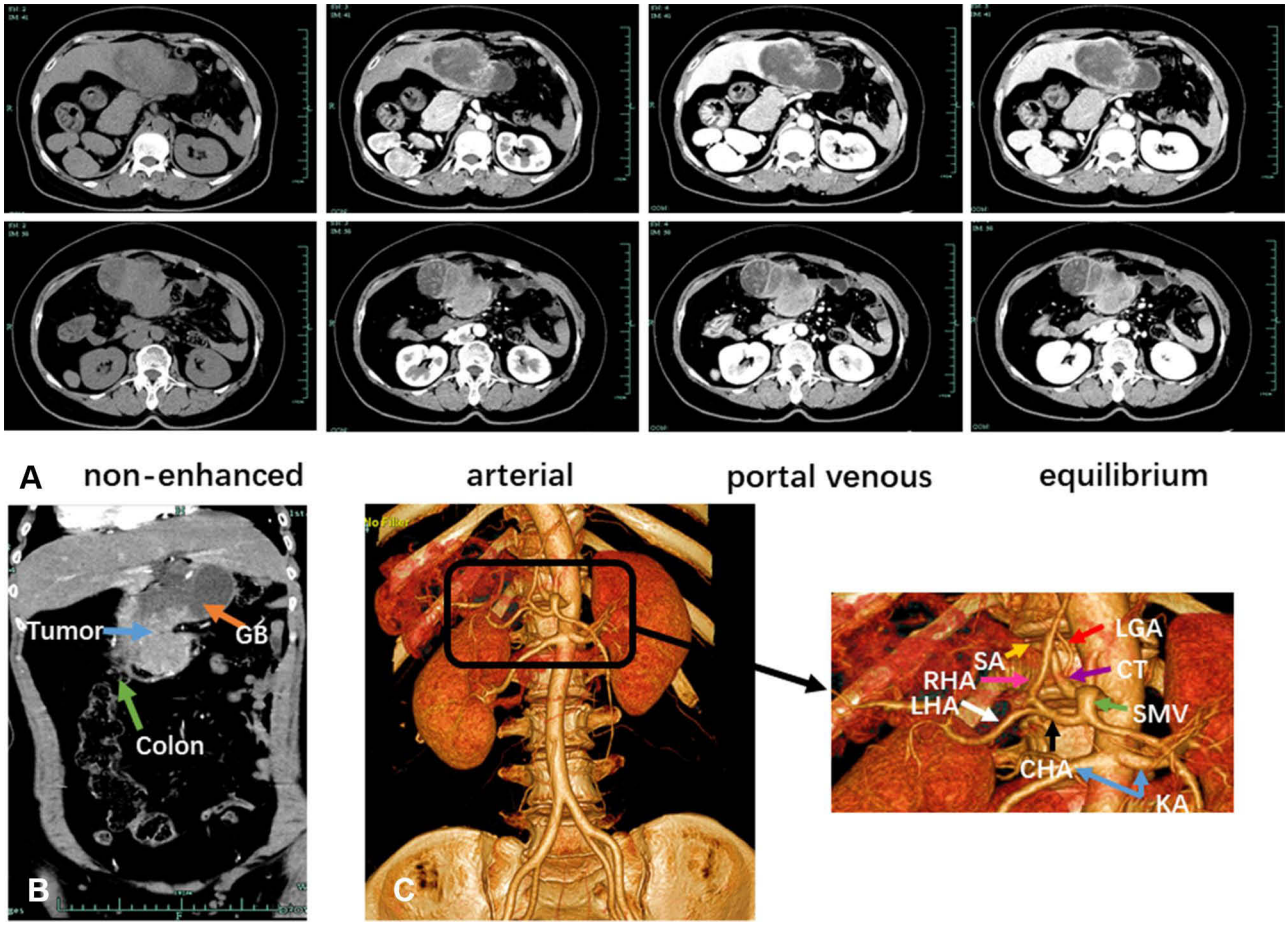

Figure 2 Preoperative CT scan indicated the diagnosis of gallbladder cancer in the SIT setting. (**A**) The CT images in the non-enhanced, arterial, portal venous, and equilibrium phases. (**B**) The coronal view showing tumor's involvement of transverse colon. (**C**) The CT angiography demonstrating significant vascular abnormalities.
Abbreviations: GB, gallbladder; 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.

the celiac trunk only divides to the splenic artery and the left gastric artery, while the common hepatic artery originates from the superior mesenteric artery. The other malformation was polysplenia syndrome, where three spleens with a similar size were presented. Polysplenia syndrome is often associated with multiple visceral and vascular abnormalities.[16] These two malformations brought higher risks of intraoperative complications associated with incomprehension of the anatomical variations. In this case, a right-handed surgeon was also in the right side on the patient, although the patient was in the SIT setting. The source and destination of all blood vessels, especially arteries must be cleared before ligation and disconnection, since huge changes of the structure and location of vascellum.

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 patients.[15] Meanwhile, the DNAH11 mutations are also associated with esophageal squamous cell carcinoma, ovarian cancer, and breast cancer.[17,18] Another DNAH family member DNAH5, a SIT-related gene, was found to be mutated in several malignancies.[19–21] Inversin, whose mutations cause an autosomal recessive cystic disorder characterized by SIT, functions as a molecular switch between Wnt signaling pathways,[22] as the Wnt pathways has close relationship with carcinogenesis including development of gallbladder cancer.[23,24]

Therefore, it is possible that the mutations in SIT also 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

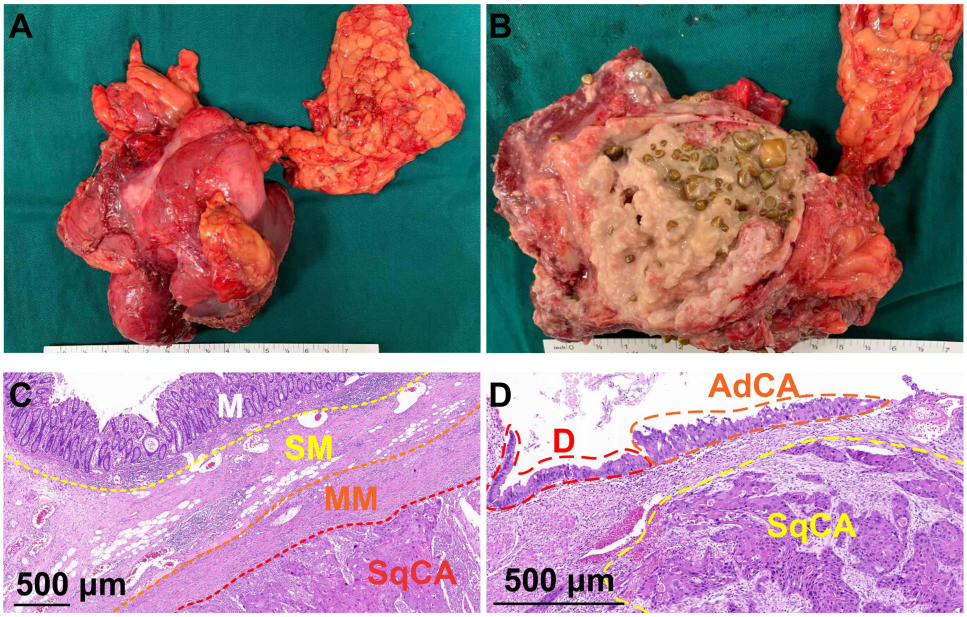

Figure 3 Pathology studies confirmed the diagnosis of gallbladder cancer. (**A**) The resected sample with adjacent colon and liver tissues. (**B**) Cross-sectional profile showing huge gallbladder mass and multiple gallstones. (**C**) H & E staining showing tumor's involvement of colon. (**D**) H & E staining of gallbladder adenosquamous carcinoma.
Abbreviations: M, mucosa layer; SM, submucosa layer; MM, muscular layer; SqCA, squamous carcinoma; D, dysplasia in gallbladder glandular epithelium; AdCA, adenocarcinoma.

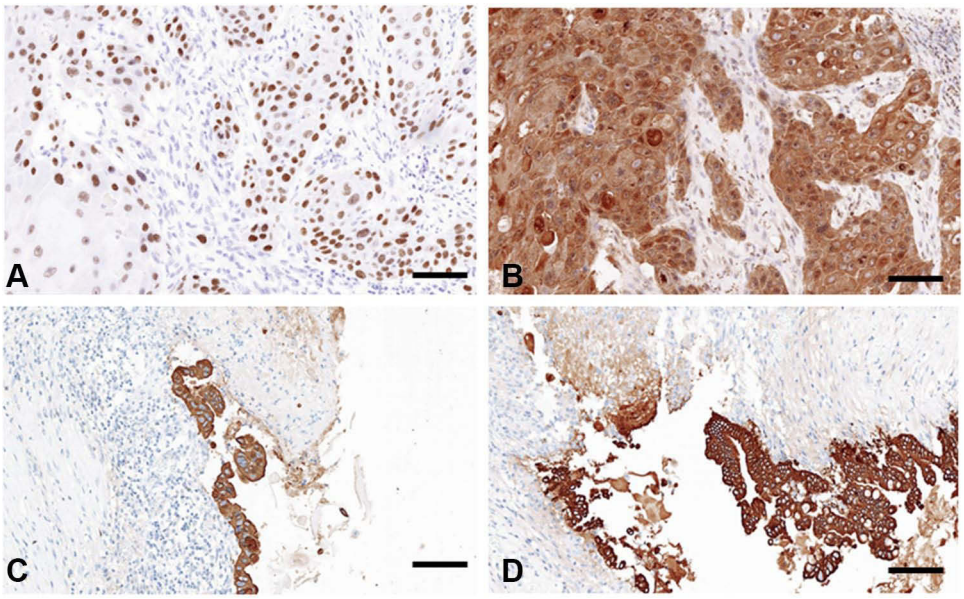

Figure 4 Immunohistochemistry assays suggested (**A**) positive P63, (**B**) positive CK5/6, (**C**) positive CK7, and (**D**) positive CK19 expression. The scale bars indicate 100 μm.

that gallbladder carcinoma, a highly malignant disease with poor prognosis,[25] could also be an unfortunate outcome of SIT. Specifically, our pathology diagnosis is adenosquamous carcinoma, a relatively rare type across gallbladder malignancies,[26,27] especially in a SIT setting. Compared to adenocarcinoma, adenosquamous carcinoma is likely to develop a more advanced stage with rapid progression and declined prognosis.[28] Optimistically, the survival data of resectable adenosquamous gallbladder cancer is comparable to that of gallbladder

adenocarcinoma after successful radical surgical resection.[29,30] Therefore, radical resection is the preferred treatment for this patient and similar cases.[31,32]

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, helped evaluate the visceral malformations, which eventually facilitated surgery success. The SIT population should receive regular surveillance to detect early and improve long-term survival in case malignancies occur.

Abbreviations

SIT, situs inversus totalis; CK7, cytokeratin 7; CK19, cytokeratin 19, CK5/6, cytokeratin 5/6; CT, computed tomography.

Data Sharing Statement

All data generated or analysed during this study are included in this article.

Ethics Approval and Consent to Participate

Ethics approval and consent was approved by Ethics Committee of First Affiliated Hospital, Zhejiang University School of Medicine.

Consent for Publication

Patient consent form had signed by patient.

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We are very grateful to the patient for her support of clinical data collection.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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Disclosure

There are no competing interests.

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