

Date: Dec 12, 2018

Dear Editor and Reviewer,

I hope this email finds you in good health and high spirit.

Here is a manuscript by Bing-jie Lu, Xue-dong Cao, Nong Yuan, Ning-ning Liu, Nisma L Azami, and Ming-yu Sun entitled **“Concomitant adenosquamous carcinoma and cystadenocarcinoma of the extrahepatic bile duct: A Case Report”**, as a “case report” publication on World Journal of Clinical Cases.

I really appreciate for your effort for your excellent job to our manuscripts. I thank Editors and Reviewers so much for their thoughtful comments and very detailed, specific suggestions. The reference styles and running title have been carefully checked. Thorough and extensive revisions have been made throughout the manuscript.

Thank you very much for your patience and kindness.

Reply to Reviewers' Comments

Review 02510721: To Authors The case report is very interesting for its clinical relevance. In the manuscript are reported a lot of informations about the clinical, diagnostic and pathological features of the case.

Suggestion 1:

Should be useful to refer more details on the surgical procedure employed.

Answer:

I have already added the details of the surgery: The patient underwent radical surgery for hilar cholangiocarcinoma and resection of choledochal cyst.

During surgery, the EHBD was found obviously thickened by approximately 5 cm and there was a 3 cm mass-like structure in the lower common hepatic duct, which penetrated the wall without invading the serosa. Enlarged hilar lymph nodes or gallbladder stones were not observed. No metastases were

found in the liver, spleen, and other abdominal organs. Also, there is no evidence of local metastatic involvement of the regional lymph nodes. Thus, no hepatectomy, pancreatectomy or lymphadenectomy was performed. Intraoperative frozen section was done to examine proximal and distal margin status, and all the resection margins were free of residual cancer cells. The operation lasted for more than 4 hours, and the intraoperative blood loss was about 300 ml. No blood transfusions was given.

Suggestion 2:

In the discussion there is the confusion in the presentation of the various informations and it needs of major organization in the exposition, with separation of each section: diagnostic features, pathological characteristics of the lesions, indications of the therapeutic approach, clinical evolution after the treatment and outcomes. In summary the manuscript needs of major revision.

Answer:

Under the heading of Discussion, the following five paragraphs have been presented in this order:

- 1) Epidemiological characteristics
- 2) Diagnostic features
- 3) Pathological characteristics
- 4) Treatment and outcome
- 5) Summary

Review 03034605: The authors have described an interesting case of concomitant ASC and cystadenocarcinoma of bile duct. however, there are several important details missing in the manuscript. 1. Please mention the details of the surgery performed.

Question 1:

Did it involve hepatectomy or pancreatectomy? Was lymphadenectomy performed?

Answer:

No metastases were found in the liver, spleen, and other abdominal organs. Also, there is no evidence of local metastatic involvement of the regional lymph nodes. Thus, no hepatectomy, pancreatectomy or lymphadenectomy was performed.

Question 2:

Was intraoperative frozen section done to examine proximal and distal margin status?

Answer:

Intraoperative frozen section to examine proximal and distal margin status was performed.

Question 3:

What was the operative time and blood loss? Was intraoperative blood transfusion given?

Answer:

The operation lasted for more than 4 hours, and the intraoperative blood loss was about 300 ml. No blood transfusion was given.

Question 4:

Why was the hospital stay 21 days? Please mention in details about the postoperative complications.

Answer:

In view of the patient's physical condition, surgery was performed 1 week after admission. The postoperative complications include bleeding, bile leakage, infection, and liver failure. Although the patient did not have the above mentioned serious complications, the general anesthesia was traumatic and the patient's physical condition was not good, so it is recommended to stay in hospital for observation.

Question 5:

What was the status of the resection margins in the histopathology?

Answer:

All the resection margins were free of residual cancer cells.

Question 6:

Was any adjuvant therapy given to this patient?

Answer:

The patient received a combination of postoperative analgesia and prophylactic antibiotics.

Question 7:

Please conduct detailed literature review and describe the key features of such concomitant bile duct tumors in tabular format.

Answer:

Literature describing multiple synchronous tumors of biliary tree is very limited.

Ref ere nce	Ye ar	Ag e	Ge nd er	Tumor 1	Tumor 2	Treatmen t	Outcome and follow-up
1	199 3	59	Ma le	adenosquamous carcinoma of the common bile duct	early adenocarcinoma of the gall-bladder	Surgery	Unknown
2	200 5	48	Ma le	adenosquamous carcinoma of the common	adenocarcinoma of the common bile duct	Surgery	Deteriora tion

				bile duct			
3	201	67	Ma	squamous cell	adenocarcinoma of	Surgery	Death
	5		le	carcinoma of the	the extrahepatic		
				extrahepatic bile	bile duct.		
				duct.			
4	201	50	Fe	adenocarcinoma of	intrapancreatic	Surgery	No
	6		ma	the gall bladder	portion of the		recurrenc
			le		common bile duct		e
5	201	45	Ma	adenosquamous	Adenocarcinoma of	Surgery	No
	8		le	carcinoma of	Common Bile Duct		recurrenc
				gall-bladder			e

Reference:

- 1 Hayashi N, Yamaguchi Y, Ogawa M. Concomitant adenosquamous carcinoma of the common bile duct and early adenocarcinoma of the gall-bladder. *J Gastroenterol Hepatol* 1993;8:607-612 [PMID: 8280849]
- 2 Albagli R, Tsunoda A, Dececcobaldissera R, Arcuri R, Pacheco J, Dias J. Concomitant adenosquamous carcinoma and adenocarcinoma of the common bile duct: A case report. *Journal of Gastrointestinal Surgery* 2005;4:590-590.
- 3 Yoo Y, Mun S. Synchronous double primary squamous cell carcinoma and adenocarcinoma of the extrahepatic bile duct: a case report. *J Med Case Rep* 2015;9:116 [PMID: 25986701 PMCID: PMC4453035 DOI: 10.1186/s13256-015-0600-1]
- 4 Kodaganur S, Hosamani IR. Synchronous malignancies of the gall bladder and common bile duct: a case report. *World J Surg Oncol* 2016;14:106 [PMID: 27059701 PMCID: PMC4826526 DOI: 10.1186/s12957-016-0848-y]

5 Varshney VK, Rao M, Soni SC, Sureka B. Synchronous Adeno-squamous Carcinoma of Gallbladder and Adenocarcinoma of Common Bile Duct: Twin Trouble. J Gastrointest Cancer 2018; [PMID: 30397857 DOI: 10.1007/s12029-018-0177-1]

Review 00071220: I had the opportunity to review a paper “Concomitant adenosquamous carcinoma and cystadenocarcinoma of the extrahepatic bile duct: A case report”, and I found very interesting. There is no problem to publish the manuscript.

Answer:

Thank you very much for your attention and consideration to our manuscript for potential publication.

Best regards

Sincerely yours,

Ming-yu Sun Professor, M.D. & Ph.D.

Institute of Liver Diseases, ShuGuang Hospital,

Shanghai University of TCM.

No.528 Zhangheng Road

Zhangjiang Hi-Tech Park,

Shanghai, China, 201203

Tel: 86-21-20256520

Fax: 86-21-20256521

Email: mysun248@hotmail.com