

Dear editor and reviewers:

Thank you very much for all the helpful suggestions. We have extensively revised the whole manuscript.

**Reviewer #1:**

**Scientific Quality: Grade D (Fair)**

**Language Quality: Grade C (A great deal of language polishing)**

**Conclusion: Major revision**

**Specific Comments to Authors:** Feng et al. presented a case of a patient with SICC treated with Huaier granules as an adjuvant treatment after surgery. The patient was a 69-year-old Chinese man admitted to our hospital in December 2014 due to intermittent right upper abdominal pain for one month and a 4-pound weight loss. Abdomen magnetic resonance imaging (MRI) and MRCP showed multiple stones in the intrahepatic and extrahepatic bile ducts accompanied by dilatation of the intrahepatic and extrahepatic bile ducts. No CT images available before surgery. Surgical resection was performed. rapid frozen-section biopsy analysis indicated that the tumor was malignant. The authors performed radical hepatectomy combined with regional lymphadenectomy. Immunohistochemical staining showed that atypical cells in the tumor were positive for pan-cytokeratin (CK-pan) and vimentin but negative for hepatocyte paraffin 1 (HepPar-1). Taken together, these findings indicated a final definitive diagnosis of SICC. After surgery, the patient had been taken Huaier granules (20g tid po) as anti-cancer therapy. There are some controversial issues in the diagnosis and treatment of this case;

**1- Why did you perform surgery quickly without confirming the diagnosis of MRI ?CT?Ultrasonography?**

**2- According to current medical literature we know that sarcomatous change often occurs in several epithelial tumors (including HCC). Did you confirm the histopathologic diagnosis of the case? Did you use hepatocellular carcinoma markers such as Glypican-3 or did you confirm the SICC diagnosis with a liver histopathology specialist?**

**3- The Huaier granules in preventing the development of tumor recurrence should not be determined by a case report. Please revise the title, abstract and main text. Thank you for giving opportunity to review this case report.**

**R:** We thank the reviewer's constructive comments.

1. There was no indication of obvious intrahepatic bile duct neoplastic lesions by the tumor marker and the abdominal ultrasound (Moderate echo in the right lobe of liver: consider inflammatory changes) of the patient. And the abdomen magnetic resonance imaging (MRI) and MRCP showed multiple stones in the intrahepatic and extrahepatic bile ducts accompanied by dilatation of the intrahepatic and extrahepatic bile ducts. So we performed the surgery by the diagnosis of right intrahepatic bile duct stones and extrahepatic bile duct stones. However the diagnosis of sarcomatoid intrahepatic cholangiocarcinoma was found during surgery by biopsy.

2. SICC was diagnosed by pathological immunohistochemistry by liver histopathology specialist: Immunohistochemical staining showed that atypical cells in the tumor were positive for pan-cytokeratin (CK-pan) and vimentin but negative for hepatocyte paraffin 1 (HepPar-1). So it was not derived from HCC (HepPar-1 was negative)

3. Our article is a case report, not clinical research. we only found that the Huaier granules was effective to SICC in this case, and in the part of discussion we statement that 'this was the first study to use Huaier granules as a postoperative adjuvant treatment for SICC; the efficacy of Huaier granules remains unclear and needs to be further studied'. So, the title of our case report is just a description of a treatment method for colleagues to share and discuss, but it does not prove that Huaier Granules have specific effects on SICC.

**Reviewer #2:**

**Scientific Quality: Grade C (Good)**

**Language Quality: Grade B (Minor language polishing)**

**Conclusion: Accept (General priority)**

**Specific Comments to Authors:** Congratulations for the diagnosis and the treatment of incidental SICC. But are you sure about the effectiveness of the Hauier granules for SICC after surgery, because your case is an early stage SICC maybe no extra treatment is needed for this tumor?

**R:** We thank the reviewer's constructive comments.

Based on the fact that there is no other treatment for SICC other than surgical resection, this article attempts to explore new treatments for this type of disease, and truthfully describes a treatment method for colleagues to share and discuss. The efficacy and mechanism of Huaier granules remains unclear and needs to be further studied by clinical research. An early stage SICC may need no extra treatment after operation, So it needs our further research. Here, we only truthfully described a treatment method for the SICC after surgery in the form of case report in order to share and discuss together.

**Reviewer #3:**

**Scientific Quality: Grade C (Good)**

**Language Quality: Grade B (Minor language polishing)**

**Conclusion: Major revision**

**Specific Comments to Authors:** The authors have presented an interesting case of incidentally detected Sarcomatoid intrahepatic cholangiocarcinoma treated successfully by liver resection. I have following comments regarding the manuscript.

1. The role of Huaier granules in preventing the development of tumor recurrence cannot be determined by this single case report. Please revise the title, abstract and main text accordingly.

2. Why the tumor lesion not visible on MRI?

- 3. Was contrast enhanced computed tomography of the abdomen done preoperatively? If not then why?**
- 4. What was the Hepatitis C virus status of this patient?**
- 5. Please mention which hepatectomy was done - right, right extended, segmental?**
- 6. Please add the operative time, intraoperative blood loss and duration of hospital stay after surgery.**
- 7. Did the patient had recurrent pyogenic cholangitis which predisposed to the development of intrahepatic cholangiocarcinoma?**
- 8. What was the histological finding of the adjoining non-tumorous liver in the resected specimen? Did it show cirrhosis or any other liver disease?**

**R:** We thank the reviewer's constructive comments.

1. Our article is a case report, not clinical research. we only found that the Huaier granules was effective to SICC in this case, and in the part of discussion we statement that 'this was the first study to use Huaier granules as a postoperative adjuvant treatment for SICC; the efficacy of Huaier granules remains unclear and needs to be further studied'. So, the title of our case report is just a description of a treatment method for colleagues to share and discuss, but it does not prove that Huaier Granules have specific effects on SICC.
2. In our case, it might be an early stage SICC and could not be discovered by MRI. Or the tumor lesion might be covered by stones. However, the tumor lesion was found during operation, and confirmed by immunohistochemistry.
3. The contrast enhanced computed tomography of the abdomen was not done preoperatively, which might be a shortcoming of this case. However, there was no indication of obvious intrahepatic bile duct neoplastic lesions by the tumor marker and the Abdominal ultrasound(Moderate echo in the right lobe of liver: consider inflammatory changes) of the patient. And the abdomen magnetic resonance imaging (MRI) and MRCP showed multiple stones in the intrahepatic and extrahepatic bile ducts accompanied by dilatation of the intrahepatic and extrahepatic bile ducts. During surgery, the bile duct wall of the right anterior lobe was thickened, and a mass was visible in the duct by choledochoscopy. Then, the rapid frozen-section biopsy analysis indicated that the mass was malignant.
4. The Hepatitis C antibody IgG was negative, which is added in the article.
5. We performed right hepatectomy combined with regional lymphadenectomy, and no evidence of cancer infiltration was found at the margin of the hepatectomy by histopathological examination. Which is mentioned in the article.
6. The operative time(four hours and a half), intraoperative blood loss(300ml), and duration of hospital stay after surgery(16 days) are all added in the article.
7. In our study, the patient presented with intermittent right upper abdominal pain for one month as the primary symptom, which may indicated that biliary infection caused by intrahepatic and extrahepatic biliary stones. And the inflammatory irritation caused by bile duct stones may be related to SICC, but the precise pathological mechanism that leads to SICC is unknown, and need further research.
8. The histological finding of the adjoining non-tumorous liver in the resected

specimen was: a large number of inflammatory cell infiltration, multinucleated giant cell reaction and small bile duct hyperplasia. No cirrhosis or other liver disease was found.

**Reviewer #4:**

**Scientific Quality: Grade B (Very good)**

**Language Quality: Grade B (Minor language polishing)**

**Conclusion: Accept (General priority)**

**Specific Comments to Authors: Overall interesting report and well written. Need bit of language revision.**

**R:** We thank the reviewer's constructive comments. We have made the language revision.