

Hepatocellular carcinoma with indocyanine green excretory defect: a case report and review of the literature

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Abstract

Constitutional indocyanine green (ICG) excretory defect is rare. However, ICG excretory defect concomitant with hepatocellular carcinoma (HCC) is extremely rare, and only six reports of hepatectomy in patients with constitutional ICG excretory defect have been published in the English language literature through 2020. In this study, we report a case of combined HCC and ICG excretory defect and discuss its clinicopathological features and outcomes. The case featured a 68-year-old man who was admitted to the hospital with a diagnosis of resectable HCC. The preoperative ICG retention rate at 15 minutes was 82.9%. Despite this finding, the Child–Pugh assessment and hepatobiliary-specific magnetic resonance imaging (MRI) did not reveal any abnormal findings. Therefore, we diagnosed the patient with constitutional ICG excretory defect and performed partial hepatectomy. For patients requiring hepatectomy, the indications and procedure for surgery should be considered. These should be based on liver function tests such as gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid-enhanced MRI.

Keywords

Indocyanine green, hepatocellular carcinoma, Gd-EOB-DTPA, hepatectomy, Child–Pugh classification, excretory defect

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Introduction

Indocyanine green (ICG) is a relatively non-toxic and unstable compound. ICG elimination serves as a diagnostic and prognostic tool in two areas. First, ICG is used for perioperative liver function monitoring during major hepatic resection and liver transplantation. In addition, ICG has a role in critically ill patients in the intensive care unit, in which it is used to predict mortality and assess the severity of acute liver failure or intra-abdominal hypertension.¹⁻³ Numerous studies demonstrated that ICG elimination in these patient populations can provide diagnostic or prognostic information to clinicians.⁴

Only six reports of hepatectomy in patients with constitutional ICG excretory defect have been published in the English language literature through 2020 (Table 1).⁵⁻¹⁰ In this study, we report a case of hepatocellular carcinoma (HCC) concomitantly with ICG excretory defect and discuss its clinicopathological features and outcomes. The case report is reported according to the relevant EQUATOR network guideline.¹¹

Case report

A 68-year-old non-smoking Chinese man was referred to our hospital because of a 7-day history of focal liver lesions. He had no drinking history. Gadolinium-enhanced magnetic resonance imaging revealed that the upper segment of the right anterior lobe of the liver had a slightly longer T1 signal and a slightly longer T2 signal shadow. Diffusion-weighted imaging revealed a high signal with a clear boundary, and the diameter was approximately 35 mm. The enhanced scan disclosed an obvious arterial phase. No enhancement was detected in the venous or delayed phase, and the hepatobiliary-specific phase featured a low signal (Figure 1).

Table 1. Previously reported cases of hepatectomy with constitutional indocyanine green excretory defect.

Number	First author	Year	Age/ sex	Child-Pugh grade	ICG R15	Histology	Preoperative liver functional evaluation	Treatment	Postoperative complications
1	Hanazaki ⁵	2000	47/F	ND	59.8	HCH	GSA liver scintigraphy	Left lateral sectionectomy	None
2	Yamanaka ⁶	2001	61/M	A	72	HCC	GSA liver scintigraphy, liver biopsy	Partial hepatectomy (S8)	None
3	Kadono ⁷	2006	78/F	A	79.3	IBC	GSA liver scintigraphy, AKBR	Left hepatectomy	None
4	Maeda ⁸	2007	69/F	A	83.8	HCC	BTR	Right anterior sectionectomy	None
5	Aoki ⁹	2013	77/M	B	77.1	HCC	GSA liver scintigraphy	Left medial sectionectomy + resection of the ventral region of the anterior segment	Hyperbilirubinemia
6	Richi ¹⁰	2018	83/M	A	76.2	HCC	GSA liver scintigraphy	Partial hepatectomy (S4)	None

ICG R15, indocyanine green retention rate at 15 minutes; F, female; M, male; HCH, hepatic cavernous hemangioma; IBC, intrahepatic biliary cystadenoma; HCC, hepatocellular carcinoma; AKBR, arterial ketone body ratio; GSA, 99mTc-galactosyl human serum albumin; BTR, branched chain amino acid and tyrosine ratio; ND, not described.

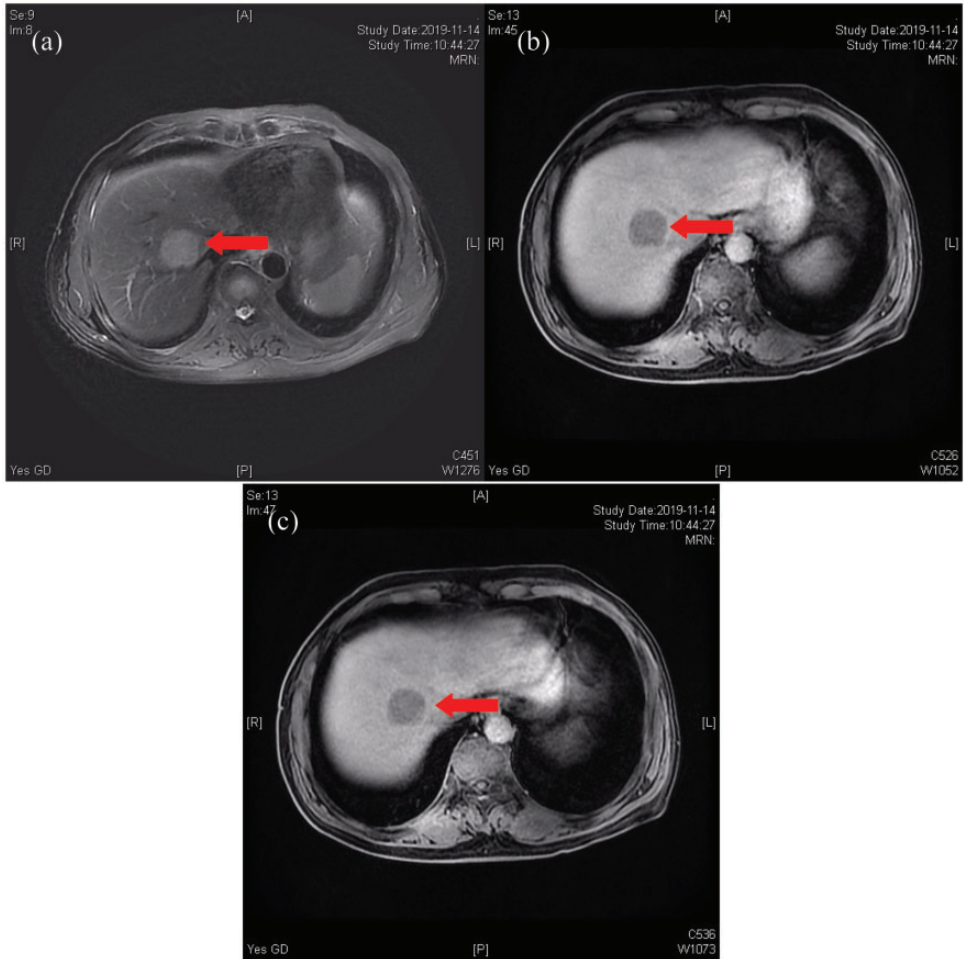


Figure 1. Magnetic resonance imaging enhanced using the liver-specific contrast agent gadolinium revealed high signal intensity in liver lesions (a), venous phase lesions displayed reduced enhancement (b), and hepatobiliary-specific phase lesions exhibited low signal intensity (c).

Surgery was planned for diagnosis and treatment. In a preoperative ICG test, the ICG retention rate at 15 minutes (ICG R15) was 82.9%. The ICG plasma clearance rate was 0.02/minutes. The patient's total bilirubin level was 1.1 mg/dL, and his direct bilirubin level was 0.3 mg/dL. His serum albumin level was 4.9 g/dL and prothrombin activity rate was 94.2%. The Child-Pugh (CP) score was 5 points, which indicated a grade of A. The surgery was canceled, and the patient was asked to

remain in bed. The ICG test was repeated after 2 days. The results illustrated that the ICG plasma clearance rate was 0.02/minutes, and ICG R15 was 84.9%.

Despite this finding, the CP assessment and gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid (Gd-EOB-DTPA)-enhanced MRI did not reveal any abnormal findings, and there was no background disease. Antibodies against hepatitis C virus and hepatitis B virus surface antigen were negative. The levels of the serum tumor

markers alpha-fetoprotein (AFP), carcino-embryonic antigen, and cancer antigen 19-9 were within the normal ranges. Therefore, we diagnosed the patient with constitutional ICG excretory defect and HCC and decided to perform radical surgery. Therefore, the patient underwent partial hepatectomy (S8). After the operation, the postoperative course was uneventful, and the patient was discharged on the seventh postoperative day. The patient remains in a good general condition.

Postoperative pathological analysis of the tumor led to a diagnosis of moderately differentiated HCC (Figure 2a). The pseudo-adenoid tumor was $4 \times 3.8 \times 3$ cm³. Other features of the lesion were as follows: vascular tumor thrombus (+, M1), nerve invasion (–), and chronic hepatitis (G1S1). The immunohistochemical results were as follows: CD (–), CK19 (–), CK7 (–), GPC3 (partly +), arginase-1 focus (+), hepatocyte (+), increased neo-vascularization in the tumor according to CD34 expression, GS (+), D2-40 (+), and AFP (–).

Discussion

Liver reserve function refers to the sum of viable and functional liver parenchymal cells, which can reflect the potentially

effective functional state of the liver.¹² ICG is mainly accumulated by hepatocytes and excreted mainly through the carrier system via the bile duct, and it does not enter the intestinal circulation after excretion.¹³ In normal liver tissue, ICG can be quickly accumulated by hepatocytes after entering the blood, and it can exhibit fluorescence after being excited by external light. After ICG is excreted through the biliary system, the fluorescence will gradually fade. In liver tumor tissues, portal vein uptake function is preserved, whereas the biliary excretion function of ICG may be impaired, leading to its accumulation. During surgery, ICG accumulation and fluorescence can be observed in the surrounding tissues of the tumor, but the specific mechanism has not been confirmed. These features may be related to changes in the liver microenvironment caused by tumor compression or tumor progression.¹⁴ The ICG clearance test is currently one of the most widely used and accurate methods for evaluating liver reserve function.¹⁵ ICG R15 is important for estimating hepatic functional reserve and the selection of the appropriate surgical procedure before hepatectomy.

Hepatectomy in cases of constitutional ICG excretory defect is exceedingly rare. Only six reports of hepatectomy in patients

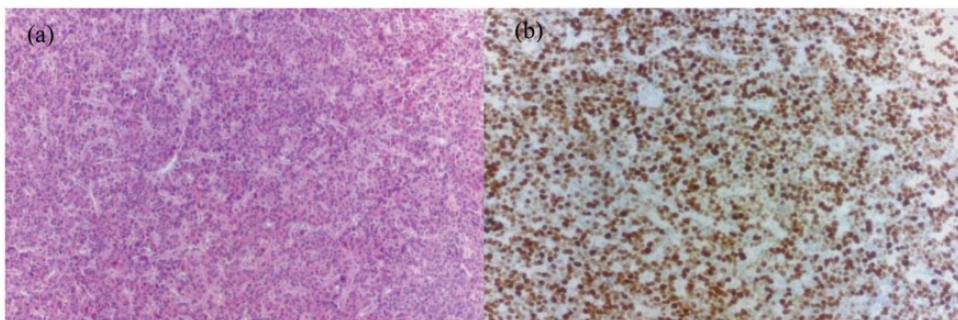


Figure 2. Microscopic findings (hematoxylin–eosin staining, $\times 200$). (a) Expansion of perisinusoidal cells and an atrophic hepatic cord in the background of liver tissue can be observed. (b) Immunohistochemical staining ($\times 100$) illustrated that the proliferation index of Ki-67 was relatively high.

with this defect have been reported. Among these cases, only four patients had HCC.^{6,8–10} Two other patients had cavernous hemangioma and biliary cystadenocarcinoma, respectively.^{5,7} All of the patients were Japanese. To the best of our knowledge, constitutional ICG excretory defect has only been reported in Japan. This report marks the first identification of this defect in another country. This disease does not feature any clinical symptoms. Therefore, unless ICG tests are performed regularly, it is likely that this disease will not be observed. Compared with the findings of previous cases, this case was more typical, and it provides a template for the diagnosis of this disease in the future.

^{99m}Tc-galactosyl human serum albumin (GSA) liver scintigraphy has been hypothesized to be the best modality for evaluating hepatic functional reserve.⁸ Aoki et al.⁹ reported that patients with Dubin–Johnson syndrome and ICG excretory defect should be analyzed via GSA scintigraphy to ensure the safety and success of hepatectomy. GSA scintigraphy provided a more accurate representation of hepatic functional reserve in our case, which is why Japanese doctors used it to evaluate the predictive score. In this case, we chose to use Gd-EOB-DTPA-enhanced MRI for the preoperative evaluation of the patient. After intravenous injection, Gd-EOB-DTPA binds to albumin in blood, but this binding is relatively weak. Therefore, the contrast agent only remains in the blood for a short time before being specifically accumulated by hepatocytes.¹⁶ Gd-EOB-DTPA, ICG, and bilirubin have roughly the same metabolic pathways in the liver and compete for the same carrier.¹⁷ Gd-EOB-DTPA-enhanced MRI can be used to assess the reserve function of the liver and calculate the liver volume simultaneously. Gd-EOB-DTPA-enhanced MRI has diagnostic utility for small HCC lesions with a diameter of ≤ 2 cm. This modality

will have broader applicability in the early diagnosis of small liver cancer with a diameter of ≤ 1 cm in the future. The relationship between Gd-EOB-DTPA-enhanced MRI findings and the degree of HCC differentiation has been extensively studied, and Gd-EOB-DTPA is expected to become a potential tool for the preoperative prediction and postoperative evaluation of HCC, which would be beneficial for improving the treatment of HCC.¹⁸ Therefore, Gd-EOB-DTPA-enhanced MRI is a potential method for the quantitative evaluation of liver reserve function.

Conclusions

Constitutional ICG excretory defect is an extremely rare disorder. At present, the surgical indications for surgery for this condition should be comprehensively considered. The results of liver function tests, such as Gd-EOB-DTPA-enhanced MRI, are important for treating this disorder.

Consent statement

This study was conducted in accordance with the declaration of Helsinki, and written informed consent was obtained from the patient.


Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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