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Case report

# Hepatocellular adenoma initially diagnosed as hepatocellular carcinoma with resistance to proton beam radiotherapy - A case report

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ABSTRACT

*Introduction and importance:* Hepatocellular adenoma (HCA) is a rare liver tumor. We report a case of a radio-resistant liver tumor that was removed surgically and found to be HCA.

*Case presentation:* A 37-year-old Japanese man was incidentally diagnosed with a liver tumor. He had no history of viral hepatitis nor metabolic disorders. MRI revealed a tumor enhancing in arterial phase, followed by washout in late phase, and hypointensity in hepatobiliary phase. A diagnosis of hepatocellular carcinoma (HCC) was made and surgery was advised. However, the patient chose proton beam radiotherapy. Although the tumor initially shrunk, it increased in size thereafter. Therefore, anterior sectionectomy was performed. Histology revealed proliferation of hepatocytes without cytologic atypia. On immunohistochemistry, CRP, SAA, GS, L-FABP, and nuclear expression of β-catenin were positive. A final diagnosis of mixed inflammatory and β-catenin activated HCA was made.

*Clinical discussion:* HCA is associated with obesity. The present case was a slightly obese man without history of viral hepatitis. In such cases, HCA should be considered. In the present case, proton beam radiotherapy was performed for a diagnosis of HCC. However, the tumor was radio-resistant.

*Conclusion:* HCA shows an almost equal male to female ratio in the Asian population. Molecular classification is vital in the management of HCA. HCC and HCA are often difficult to differentiate; tumor biopsy is necessary for patients with atypical imaging findings and in younger patients without underlying liver disease. Since the effectiveness of radiation therapy on HCA has not been reported, surgery should be preferred.

## 1. Introduction

Hepatocellular adenoma (HCA) is a rare benign liver tumor with the complications of bleeding and malignant transformation. The incidence rate of HCA is 0.07 per 100.000 population per year [1]. The use of oral contraceptives, anabolic steroids, diabetes mellitus, obesity, and glycogen storage diseases are the risk factors for the occurrence of HCA [2,3]. The molecular and pathological classification of HCA has demonstrated a distinctive genotype-phenotype correlation, as each subtype is associated with certain risk factors and complications. The 2019 WHO molecular classification categorizes HCA into six subgroups using molecular characterization and immunohistochemistry [4]: Hepatocyte nuclear factor 1α (HNF1A)-inactivated HCA (H-HCA), inflammatory HCA (I-HCA), β-catenin mutated HCA (b-HCA), mixed inflammatory and β-catenin mutated HCA (b-IHCA), sonic hedgehog activated HCA (sh-HCA), and unclassified HCA. H-HCA accounts for 30 to 40% of HCA and has a mutation of HNF1A. HNF1A inactivation in hepatocytes leads to lipid metabolic disorders, and causes a steatotic phenotype. On immunohistochemistry, there is loss of Liver-fatty acid binding protein (L-FABP). I-HCA is the most frequent subtype (40 to 50% of the cases), with the mutation of STAT3, which is a major transcription factor of inflammation. The activation of the IL-6/STAT3 signaling pathway leads to overexpression of the proteins such as serum amyloid A protein (SAA) and C-reactive protein (CRP). On immunohistochemistry, the tumor is stained by anti SAA and anti CRP antibodies. b-HCA accounts for 10 to 15% of HCA. β-catenin is an oncogene, activating the WNT/β-catenin signaling pathway, which plays a major role in the proliferation of hepatocytes. On immunohistochemistry, there is an overexpression of glutamine synthetase (GS) with a nuclear staining of β-catenin. b-IHCA demonstrates both inflammatory and β-catenin activation. The histology of b-IHCA consists of the combination of each subtype. sh-HCA has an activation of the sonic hedgehog pathway due to the fusion of INHBE and GLI1. On immunohistochemistry, Prostaglandin D2 Synthase is overexpressed.

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The subtype classification is vital in managing HCA. b-HCA and b-IHCA have higher potential for malignant transformation. European Association for the Study of the Liver clinical guidelines recommend resection of HCA in the following situations: greater than 5 cm in diameter, increasing in size, b-(I)HCA, and male irrespective of size and subtype. Men has higher risk of malignant transformation (estimated 50% in male, 5% in female) than women [5].

Herein, we report a case of b-IHCA which was surgically resected because the tumor increased in size after proton beam radiotherapy with a pre-operative diagnosis of hepatocellular carcinoma (HCC). This work has been reported in line with the SCARE 2020 criteria [6].

## 2. Presentation of case

A 37-year-old Japanese man was diagnosed with a liver tumor during a medical check-up. He had no medical history of viral hepatitis nor metabolic disorders, and had not taken anabolic steroids. On physical examination, he was slightly obese (body mass index: 26.9) but the rest of the findings were unremarkable. Ultrasonography was done and revealed a fatty liver with a 28 mm heterogeneous hypoechoic nodule located in the segment 5 of the liver (Fig. 1). Contrast enhanced-computed tomography revealed a tumor with homogenous enhancement in the arterial phase and washout in the portal and late phases. The tumor likely invaded the gall bladder. Magnetic resonance imaging (MRI) revealed a tumor with isointensity in T1 weighted imaging (T1WI), hyperintensity in T2 weighted imaging (T2WI), and hyperintensity in diffusion weighted imaging. In-phase and opposed phase T1WI revealed signal dropout. On gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid-enhanced (Gd-EOB-DTPA) MRI, the tumor was enhanced in the arterial phase, followed by the washout with peritumoral enhancement in the portal and late phases, and hypointensity in the hepatobiliary phase (Fig. 2). Because the tumor was located on the liver surface and was very close to the large bowel, we did not perform percutaneous tumor biopsy in order to avoid dissemination and injury of the other organs. We diagnosed the patient with HCC with underlying fatty liver, and recommended surgery. However, the patient chose radiation, and underwent proton beam radiotherapy at another institute. After radiation, the tumor shrunk to 20 mm in size. However, nine months later, the tumor again enlarged to 27 mm (Fig. 3). Therefore, we recommended surgery again, and the patient agreed with our plan. Ten months after his first treatment, anterior sectionectomy of the liver was done. Macroscopic findings of the surgical specimen showed a round reddish nodule with clear margin. Histology showed proliferation of hepatocytes without significant cytologic atypia. Also noted were partial steatosis, sinusoidal dilatation and bleeding. Hemosiderosis and bleeding were found in the adjacent non-tumor tissues. Immunohistochemical findings included the following; CRP(+), SAA(+), GS(+), L-FABP(+), and nuclear expression of β-catenin(+) (Fig. 4). Finally, the tumor was diagnosed as mixed inflammatory and β-catenin activated HCA. Postoperative course was uneventful. He was discharged home on postoperative day 9.

## 3. Discussion

HCA has a lower incidence in Asian countries than in the Western countries. Western reports described that HCA has higher prevalence in young women [7], while Asian reports showed that the ratio was almost equal or higher in men [8–10]. The reason for the difference among the regions may be the use of the oral contraceptives. Western women tend to take oral contraceptives more frequently than Asians. The occurrence of HCA is associated with obesity. Obesity increases estrogen exposure [3]. The numbers of patients with HCA had been increasing due to the development of imaging modalities and the increasing prevalence of obesity [10,11]. The present case is a slightly obese young Japanese man without viral hepatitis. Hence, if a liver tumor is present in an obese patient, HCA should be considered as part of differential diagnosis, even in men.

Imaging findings vary according to the subgroup, and it is sometimes difficult to differentiate HCA from other hypervascular tumors such as HCC, focal nodular hyperplasia, or angiomyolipoma. Recent studies described the imaging features of HCA in each subgroup [12–14]. In H-HCA, diffuse steatosis is seen in most cases (67.4–100%), with mild to moderate enhancement with hypointensity in the hepatobiliary phase on Gd-EOB-DTPA-MRI. In I-HCA, there is atoll sign in the fat-suppressed T2WI; a typical hyperintense rim caused by sinusoidal dilatation, which is found in 14.3–54% cases. Additionally, persistent enhancement in the portal and delayed phases are also present. Although most I-HCA cases show hypointensity in the hepatobiliary phase, some cases demonstrate iso–hyperintensity. In-b-HCA, central scar is sometimes found (55.6–56%), and iso–hyperintensity in the hepatobiliary phase is seen due to the preserved expression of OATPB1/B3 [15]. b-IHCA are likely to present with similar findings as I-HCA. In the present case, steatosis was present in the in-phase and opposed-phase T1WI, with perinodular enhancement in the portal and delayed phases. There were no atoll sign, persistent enhancement nor uptake of contrast agency in the hepatobiliary phase. We believe that it is difficult to diagnose b-HCA accurately because of the lack of the specific findings of HCA.

The European Association for the Study group of the Liver guidelines recommend resection for the following: tumor greater than 5 cm in diameter, increasing in size, b-IHCA, and if found in males irrespective of size. Ablation and embolization are recommended for poor surgical candidates [5]. The present case was diagnosed as HCC, hence surgery was recommended. However, the patient initially chose proton beam radiotherapy. The tumor initially reduced in size, but subsequently enlarged again. There has been no report about the use of radiotherapy in hepatocellular adenoma. Radiation therapy is generally indicated for

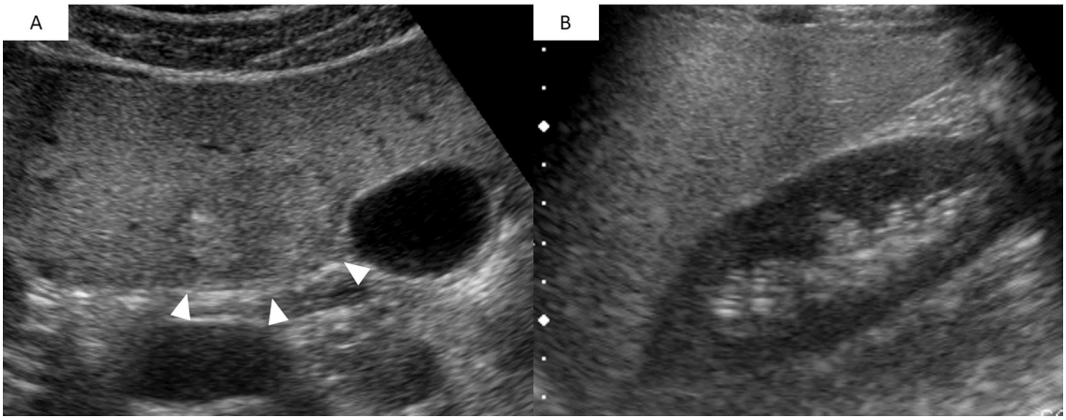


**Fig. 1.** A 28 mm heterogeneous hypoechoic nodule, located in the segment 5 of the liver (A) (arrowheads). Fatty change is also seen on ultrasonography (B).

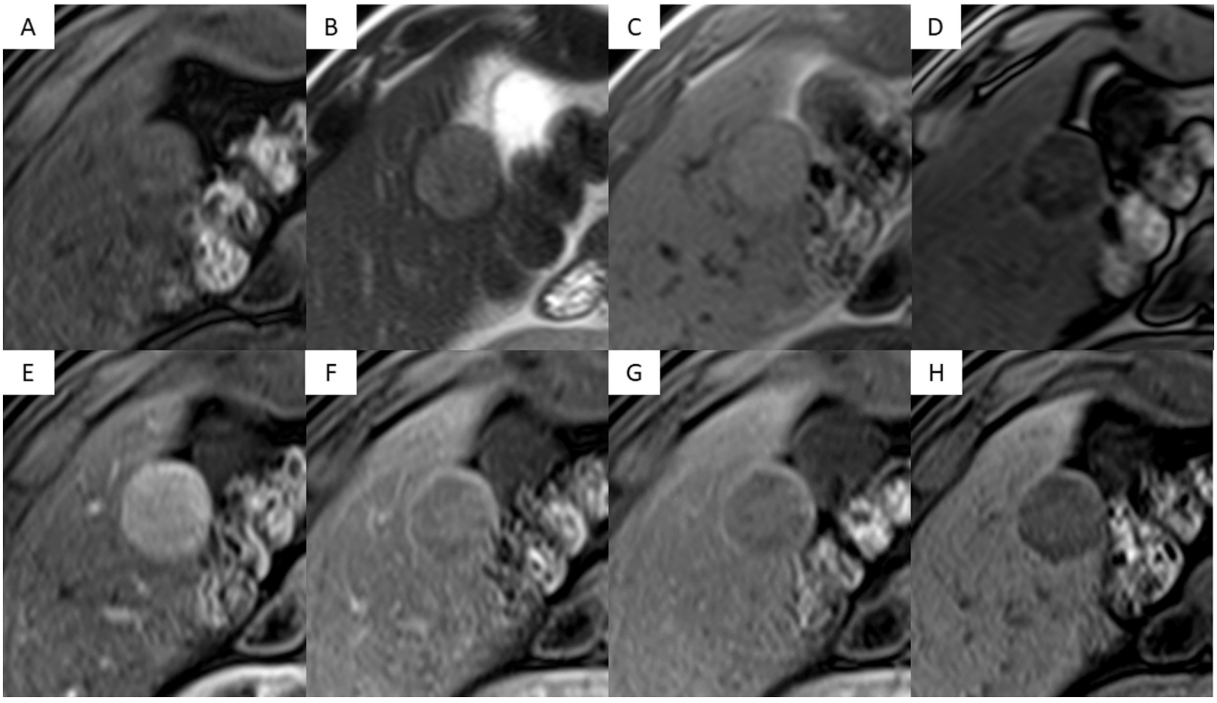


**Fig. 2.** On MRI, tumor shows isointensity in T1WI (A), hyperintensity in T2WI (B). In-phase (C) and opposed-phase (D) T1WI reveals signal dropout. Tumor is enhanced in the arterial phase (E), followed by the washout with peritumoral enhancement in the portal (F) and late phases (G), and hypointensity in hepatobiliary phase (H).

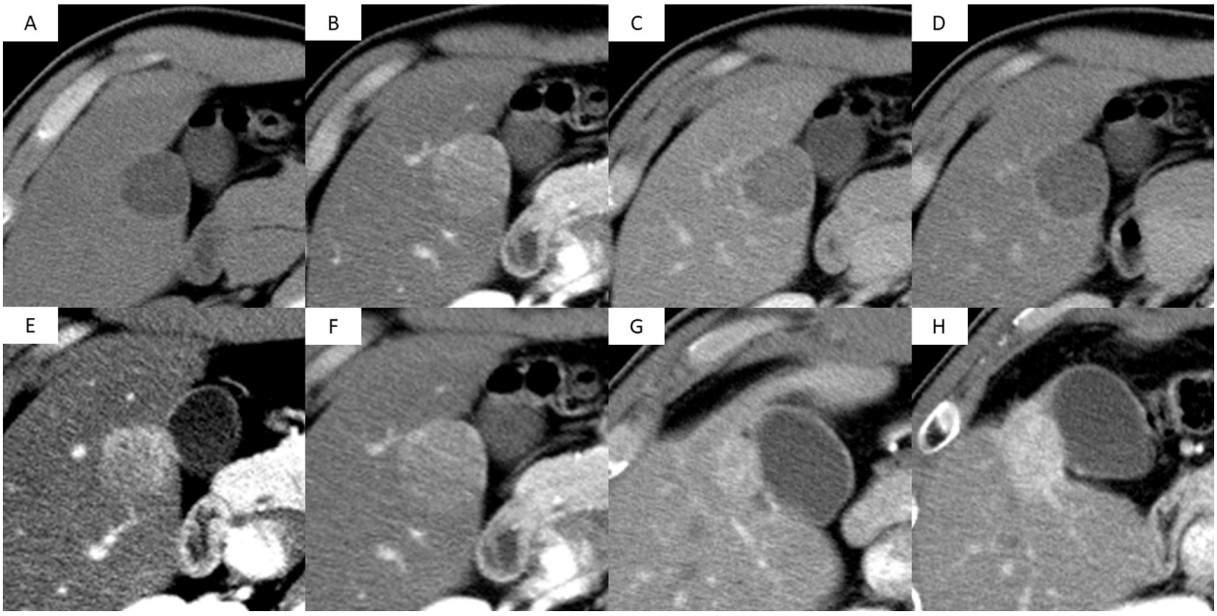


**Fig. 3.** CT showing tumor located in the segment 5 of the liver (A), which is homogeneously enhanced in the arterial phase (B), followed by wash out with perinodullary enhancement in the portal (C) and late phases (D). Likely invasion into the gall bladder is also seen (E). Before radiotherapy, the tumor was 28 × 26 mm in size (F). After radiotherapy, the tumor shrunk to 20 × 14 mm initially (B), and later enlarged to, 27 × 22 mm in size, 9 months after radiation (C).

malignant tumors and some benign tumors such as brain tumors, hemangioma, etc. In fact, the present case presented with resistance to radiation, hence resection is recommended.

## 4. Conclusion

The male to female ratio of HCA is almost equal in the Asian population. Molecular classification is vital in the management of HCA. Imaging findings are different among subgroups. In the present case, HCC was diagnosed due to the lack of the specific features of HCA, and proton beam radiotherapy was performed. However, the tumor showed resistance to radiation. HCC and HCA is often difficult differentiate; thus, we believe that tumor biopsy is necessary for patients with atypical imaging findings or younger patients without underlying liver diseases. Since the effectiveness of radiation therapy on HCA has not been reported, surgery should be preferred.

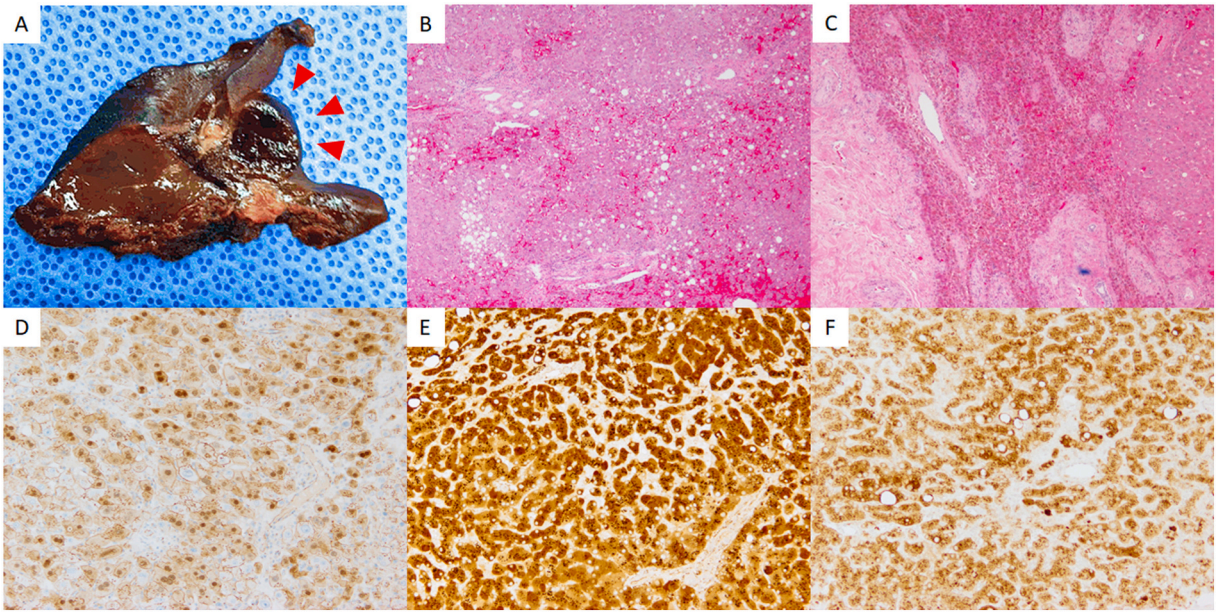


**Fig. 4.** Macroscopic findings of the surgical specimen show a round, dark reddish nodule with clear margins (A: arrowheads). Microscopically, there is proliferation of hepatocytes without cytologic atypia. Partial steatosis, sinusoidal dilatation and bleeding are also noted in the hematoxylin and esoin staining (B). Hemosiderosis and bleeding are found in the adjacent non-tumor tissues (C). Nuclear expression of β-catenin (D), C-reactive protein (E), and serum amyloid A protein (F) are positive on immunohistochemistry.

## Abbreviations

| | |
|---|---|
| b-HCA | β-catenin mutated hepatocellular adenoma |
| b-IHCA | mixed inflammatory and β-catenin mutated hepatocellular adenoma |
| CRP | c-reactive protein |
| Gd-EOB-DTPA-MRI | gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid-enhanced magnetic resonance imaging |
| GS | glutamine synthetase |
| HCA | hepatocellular adenoma |
| HCC | hepatocellular carcinoma |
| H-HCA | hepatocyte nuclear factor 1α-inactivated hepatocellular adenoma |
| HNF-1α | hepatocyte nuclear factor 1α |
| I-HCA | inflammatory hepatocellular adenoma |
| L-FABP | Liver fatty acid binding protein |
| MRI | magnetic resonance imaging |
| SAA | serum amyloid protein |
| sh-HCA | sonic hedgehog activated hepatocellular adenoma |
| T1WI | T1 weighted imaging |
| T2WI | T2 weighted imaging |

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## Ethical approval

Ethical approval was obtained from the Ethics Committee of Kurume University (No. 2021-102).

## Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

## CRediT authorship contribution statement

HK drafted the manuscript. YA and KO supervised the study. YM, TS, and TH performed perioperative management of the patient.

## Research registration

Not applicable.

## Guarantor

Hiroki Kanno.

## Provenance and peer review

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## Declaration of competing interest

Non declared.

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