CASE REPORT

Malignant transformation of hepatocellular adenoma over a decade

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SUMMARY

A 72-year-old man diagnosed with a benign hepatocellular lesion 11 years prior was referred to our hospital for an outgrowth of the tumour in liver segment 7. Extended segmentectomy was performed and the patient's postoperative course was uneventful with no recurrence for 2 years. Histopathological examination confirmed a highly differentiated hepatocellular carcinoma (HCC) coexisting with the hepatocellular adenoma (HCA), and it was suspected to have originated from the HCA. The findings from this case demonstrate that CT can be useful for detecting the transformation of HCA into HCC.

BACKGROUND

Hepatocellular adenoma (HCA) frequently affects young women taking oral contraceptives and is rare in men. The malignant transformation of HCA into hepatocellular carcinoma (HCC) is uncommon, and most cases are identified at the time of diagnosis.¹ However, it remains unclear whether HCC emerges from HCA or if the lesions are coincident. Here we report a case of a 72-year-old man who was followed-up for 11 years after diagnosis and was referred to our institution because of sudden growth of the tumour. Histopathological examination after extended segmentectomy confirmed a highly differentiated HCC coexisting with the HCA. We also describe the findings of the images collected during the various stages of growth and discuss the malignant transformation of HCA.

CASE PRESENTATION

A 72-year-old man was referred to our institution because of an outgrowth of a hepatocellular lesion located in segment 7 of the liver, which was identified during an annual medical examination 11 years prior. At that time, the tumour measured 3.5 cm in diameter. Serological tests for hepatitis B surface antigen and hepatitis C virus antibodies were negative. The patient had no history of alcohol abuse, androgenic steroid use or diabetes mellitus. The tumour was considered to be either HCA or focal nodular hyperplasia according to the findings of CT; surgical resection was not performed at that time because of its benign nature. Either CT or ultrasonography (US) was performed at subsequent annual consultations, and proximal gastrectomy was performed to diagnose Barrett's oesophageal cancer during the follow-up period. The final examination revealed the expansion of the HCA to a diameter of 11 cm. At the time of current admission, the patient's serum aspartate aminotransferase,

alanine aminotransferase and γ -glutamyl transferase levels were 30, 33 and 84 IU/L, respectively (normal ranges: 13–33, 6–30 and 10–47 IU/L, respectively). The serum albumin level was 3.5 g/dL (normal range: 4–5 g/dL) and other liver function markers were within normal limits. However, the prothrombin level was elevated to 166 mAU/mL (normal range: 0–39 mAU/mL) in the absence of vitamin K or the presence of antagonist-II (PIVKA-II); the serum α -fetoprotein level was within normal range. The fasting blood glucose level was 46 mg/dL (normal range: 70–109 mg/dL), and the body mass index was 15 kg/m² (normal range: 18.50–24.99 kg/m²).

INVESTIGATIONS

During the initial examination, the arterial phase showed a homogeneously enhanced tumour measuring 3.5 cm in diameter in the posterior section of the liver ([figure 1A](#)). However, the tumour was obscured during the late phase ([figure 1B](#)). Eight years later, CT showed heterogeneous enhancement in the arterial phase ([figure 1C](#)), with a low density relative to the surrounding area ([figure 1D](#)). After 10 years, a characteristic malignant tumour known as 'a nodule within a nodule' appeared during the arterial phase ([figure 1E](#)), with sustained enhancement in the late phase ([figure 1F](#)). The final examination showed expansion to a diameter of 11 cm ([figure 1G](#)). Low-density scar-like lesions appeared within the tumour in the delayed phase ([figure 1H](#)).

TREATMENT

Extended segmentectomy was performed. The patient's postoperative course was uneventful.

PATHOLOGICAL FINDINGS

The surgical specimen weighed 530 g and was clearly demarcated from the surrounding liver without a capsule. It was tan brown with a congested dark area ([figure 2](#)). No inflammatory changes or steatosis were observed in the background liver tissue (data not shown). Tumour histology revealed a well-differentiated HCC ([figure 3A](#)), and a HCA ([figure 3B](#)) was observed at the rim of the tumour near the surface of the liver. Immunohistochemical staining for β -catenin was positive in HCC and HCA ([figure 4A, B](#)), whereas CD34 staining was positive only in the HCC ([figure 4C, D](#)). Infiltration of CD34-positive cells was observed in the HCA ([figure 4C](#)).

OUTCOME AND FOLLOW-UP

The patient was in good health in December 2013.

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Figure 1 CT findings: (A and B) The tumour is detected as a homogeneously enhanced mass with a diameter of 35 mm in the early phase of the first examination and it is obscured in the late phase. (C and D) The tumour is heterogeneously enhanced in the early phase 8 years later and shows a low-density area in the late phase. (E and F) A nodule within a nodule pattern is observed 10 years later, with sustained enhancement. (G and H) A year later, the tumour has enlarged to 110 mm in diameter. Low-density scar-like lesions have appeared in the centre of the tumour in the late phase.

DISCUSSION

HCA is a rare benign monoclonal liver neoplasm that primarily affects women taking oral contraceptives, and its overall incidence is 3–4/10 000 in Europe and North America.² In addition to oral contraceptives, androgens, glycogenosis, tyrosinaemia and familial polyposis coli have been identified as risk factors. However, the pathogenic mechanisms underlying HCA development remain unclear, and these tumours are often encountered as an incidental finding during imaging for unrelated pathologies.

Figure 2 Fresh tumour section: the tumour is tan brown and well demarcated from the surrounding liver with no capsule. Areas of haemorrhage and irregular scarring are visible in the centre. The area of the hepatocellular adenoma was observed at the rim of the tumour (arrow head).

Patients with HCA are classified into four groups according to the correlations of their genotypes/phenotypes.³ The first group, comprising of 35–40% of all patients, almost exclusively includes women and is related to the presence of transcription factor 1 gene mutations that inactivate hepatocyte nuclear factor 1 α (HNF1 α). This group corresponds to a histologically homogeneous group of tumours characterised by marked steatosis and a very low risk of complications. The second group comprises 10%–15% of all patients, is male dominated and is characterised by the presence of mutations that activate β -catenin and cellular abnormalities. The third group includes 50% of all patients and is characterised by inflammatory HCA and serum amyloid A and C reactive protein expression. Tumours of this group usually occur in overweight women with inflammatory metabolic syndrome. The last group includes patients with unclassified tumours and represents less than 10% of all patients. HCA with activated β -catenin is reportedly associated with a greater risk of malignant transformation. Each subgroup of HCA has a pathological distinction and reflects the findings of MRI.^{4–7} HNF1 α -inactivated HCA, inflammatory HCA and β -catenin-activated HCA have been related to the MRI signs of diffuse intratumoural fat deposition, an atoll sign and a typical vaguely defined scar, respectively.⁴ HNF1-inactivated HCA and inflammatory HCA can particularly be diagnosed by radiologists with considerable accuracy.⁵

Although malignant transformation of HCA is considered rare, it has been recently reported in 4% of women and 47% of men with HCA.⁸ Men are predisposed to HCC regardless of aetiology, and many tumours in males have been shown to express androgen receptors.⁹ Therefore, surgical treatment is recommended for male patients with HCA.

Figure 3 (A) Cells in the primary tumour exhibit a high nuclear/cytoplasmic ratio and form a trabecular pattern over 3 layers. (B) Cells in the hepatocellular adenoma form an irregular trabecular patterns with two layers.

At present, no clinical or radiological assessments are available to distinguish between HCA and degenerated HCA. However, most cases of malignant transformation of HCA are recognised

at the time of diagnosis,¹ and surgical excision is usually recommended.

To the best of our knowledge, this is the first case report to demonstrate the stages of malignant transformation of HCA using CT. The tumour was isoattenuated when compared with normal liver during the non-enhanced (not shown) and delayed phases (figure 1B) of the initial CT examination, and it appeared homogeneous in the early phase (figure 1A). These findings correspond to HCA because HCA is normally composed of uniform hepatocytes with variable numbers of Kupffer cells.¹⁰ Eight years after the initial examination, the tumour was heterogeneously enhanced in the early phase (figure 1C) and hypoattenuated in the delayed phase (figure 1D). Malignant transformation was highly suspected at this point. Informed consent for liver biopsy or surgical resection could not be obtained; nevertheless, the information was reported to the patient. A nodule within a nodule is known as a sign of malignancy, and this was observed on CT performed a decade after the initial examination, although the tumour was not enlarged. A year later, the tumour had grown but remained asymptomatic. Limited available data show a possible association between the size of HCA and the risk of malignant transformation.¹ However, according to the observation that intratumoural bleeding is rare in lesions smaller than 5 cm, the size of the HCA remains the predominant criterion for determining whether resection is required.¹¹

In the present case, malignant transformation preceded tumour enlargement by 3 years. Therefore, changes in haemodynamic status may be a more important clinical sign compared with tumour size.

Marked improvements in imaging techniques, such as multi-detector row CT, dynamic MRI and contrast-enhanced ultrasound (US), allow accurate evaluation of this haemodynamic transition. In particular, contrast-enhanced US allows more sensitive recognition and specific exclusion of malignancy compared with CT or dynamic MRI.¹² Moreover, contrast-enhanced US can be repeatedly performed without the risks associated with allergic reactions or radiation exposure. In combination, these imaging modalities can be used to identify malignant transformation of HCA.

Figure 4 Immunohistochemical staining: (A and B) Overexpression of β -catenin was observed in the hepatocellular carcinoma (HCC) and hepatocellular adenoma (HCA). (C and D) CD34 staining of endothelial cells is visible in the HCC but not in the HCA. (E) CD34-positive cells have infiltrated into the HCA area.

Learning points

- ▶ Development of hepatocellular adenoma (HCA) into hepatocellular carcinoma (HCC) was visible on CT images obtained over a period of 10 years.
- ▶ Malignant transformation of HCA was reflected by haemodynamic changes prior to changes in tumour size.
- ▶ Multidetector raw CT and contrast-enhanced ultrasound can be useful for diagnosing HCA degeneration.

Contributors TT was involved in writing the article. YK assisted the surgical team during surgery. YM diagnosed the tumour.

Competing interests None.

Patient consent Obtained.

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