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CASE REPORT

Small hepatocellular carcinoma with ring calcification: A case report and literature review

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Abstract

Ring calcification in untreated hepatocellular carcinoma (HCC) is extremely rare, with only 3 previously reported cases in the English-language literature. A case of HCC with ring calcification was reported in this paper. Additionally, 3 previously reported cases of HCC with ring calcification were reviewed. In 3 of these 4 cases (including our case), surgery was performed. Although the size of the ring-calcified lesion ranged from 3.0-3.7 cm in previously reported cases, the size was only 1 cm in ours. The differentiation of the tumor was moderate in the 2 previously reported cases in the histological findings and poor in ours. In spite of their poor differentiation for their sizes, these tumors showed no early enhancement in dynamic computed tomography. All calcified tumors showed a thick fibrous capsule and extensive necrosis histologically. Ring calcification was considered to result from a circulatory disturbance caused by the imbalance between the less abundant arterial blood flow and high inner pressure induced by either the thick fibrous capsule or vigorous proliferation due to the poor differentiation. Ring calcification in untreated HCC may suggest a lower differentiation of the tumor. Even if its size is small, hepatic resection should be performed for any tumor with ring calcification because poor differentiation is considered to be one of the risk factors for recurrence after local ablation therapy, including radio frequency ablation.

Key words: Hepatocellular carcinoma; Ring calcification; Calcification in untreated neoplasms; Process of forming calcification; Histological differentiation

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INTRODUCTION

Macroscopic calcification in untreated hepatocellular carcinoma (HCC) (the term "untreated HCC" is defined as HCC that was not treated with local ablation, local injection, or embolization prior to the development of calcification) is considered rare, and has reportedly been observed in only 1.9%-3.3% of cases[1-5]. Ring calcification in untreated HCC is extremely rare, with only 3 previously reported cases in the English-language literature[6,7]. We present a case of small HCC (1 cm in diameter) showing ring calcification. To elucidate the clinical and histological characteristics of this entity, we reviewed previously reported cases of HCC with ring calcification in the English-language literature.

CASE REPORT

A 68-year-old woman with a 19-year history of chronic hepatitis C was referred for surgery because of a hepatic

tumor in segment 4 (defined by Couinaud's nomenclature for liver segmentation) (Figure 1). Despite no elevation in either the serum alpha-fetoprotein (AFP) or des-γ-carboxy prothrombin (DCP) levels and no enhancement in the dynamic computed tomography (CT) study, the tumor was suspected to be HCC from the patient's history of hepatitis C. The patient was offered surgery for the tumor but rejected the offer at that time. Six months after the first diagnosis of the tumor, the serum AFP level was elevated (128 ng/mL, but no elevation in DCP level) and the tumor showed ring calcification (Figure 1). Furthermore, an irregularly shaped tumor, which was broadly in contact with the calcified lesion and showed early enhancement in dynamic CT, was observed, whereas the calcified lesion showed no enhancement in any phase (Figure 1). After a detailed informed consent process explaining the necessity of surgery, the patient accepted the offer of surgery and underwent segment 4 segmentectomy 9 mo after the first diagnosis.

Macroscopically, a 10-mm tumor with ring calcification and an 18-mm tumor were identified in the same thick fibrous capsule (Figure 2A). Microscopic examination revealed findings of poorly differentiated HCC in the calcified lesion and moderately differentiated HCC in the non-calcified lesion (Figure 2B). Each lesion comprised only a single differentiated component and had a thick fibrous capsule (Figure 2A). With regard to the calcified tumor, extensive necrosis was diffusely observed in the tumor, suggesting that the necrosis was caused by a circulatory disturbance. The ring calcification formed inside the thick fibrous capsule (Figure 3).

The postoperative course was uneventful, and the patient is doing well without recurrence 30 mo after the surgery.

Review of the literature

A PubMed search on August 2012 for articles published since 1965 with the key words "hepatocellular carcinoma" and "calcification" yielded 62 articles published in English-language journals. These publications were all reviewed. There were only 2 articles describing 3 cases of untreated HCC with ring calcification[6,7], resulting in a total of 4 reported cases. The demographic data are shown in Table 1. The previously reported sizes of ring-calcified lesions ranged from 3.0 to 3.7, but ours was only 1 cm. Three of the four cases underwent hepatic resection. The remaining case did not receive any treatment for HCC because of markedly poor general condition, resulting in no histological confirmation for the diagnosis of HCC. Of the 3 cases for which histological findings were obtained, differentiation was moderate in the 2 previously reported cases and poor in our case. All 3 calcified lesions consisted of a single differentiated component. These 3 cases had a thick fibrous capsule, and the ring calcification formed inside the fibrous capsule. Additionally, in the previous 2 cases with histological findings, similar findings to our own case were observed; extensive necrosis was diffusely observed in the tumor[6,7].

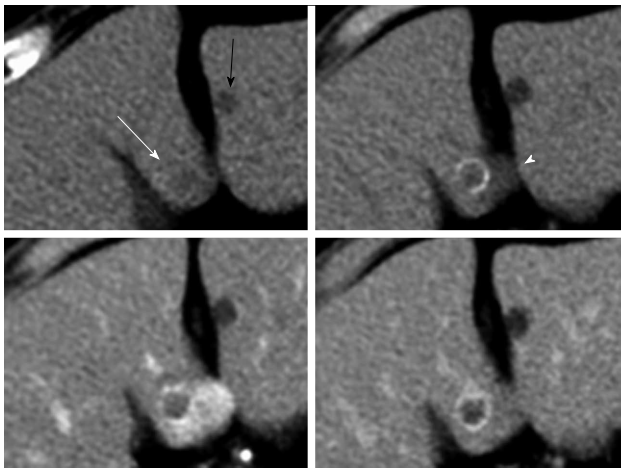

Figure 1 Findings of computed tomography. Upper left, plain abdominal computed tomography (CT) taken at the initial diagnosis revealed a 1-cm low-density lesion without calcification in liver segment 4 (white arrow). A small low-density area found in the left lateral section was a liver cyst (black arrow); upper right, plain abdominal CT taken 6 mo after the initial diagnosis revealed that the lesion had a ring calcification and an adjacent 1.8-cm lesion (white arrowhead); lower left and right, abdominal CT taken 6 mo after the initial diagnosis in the early phase (lower left) after a bolus administration of intravenous contrast material showed enhancement of the newly appeared lesion and the delayed phase (lower right) showed that it was hypoattenuated.

DISCUSSION

The cause of calcification in HCC is considered to be dystrophic calcification, in which deposition occurs locally in nonviable or dying tissues with normal serum levels of calcium and in the absence of a dysfunction in calcium metabolism[4-7]. Dystrophic calcification in untreated neoplasms is most commonly observed in meningioma, papillary thyroid carcinoma, and ovarian serous cystadenocarcinoma[8]. In such tumors, the mechanisms leading to the formation of calcifications in the tumors have been thoroughly analyzed[8]. Although the exact mechanism of calcification formation is not well understood, it has been suggested to be the following. In such tumors, spontaneous tumor necrosis occurs easily due to micro-infarction caused by their structural property, which predisposes microcirculatory disturbance. Matrix vesicles and matrix giant bodies derived from degenerated or necrotic cells sequester hydroxyapatite crystals to form seed crystals. Mineral deposition encrusts these crystals. Collagen and elastic fibers derived from degenerated basement membranes adjacent to necrotic cells are a prerequisite for the calcification to be identifiable because the expansion of hydroxyapatite deposition requires these connective tissues as nidi[8]. Namely, tumors with abundant stromal tissues, in which ischemic necrosis easily occurs, are likely to show identifiable dystrophic calcification. Therefore, the reason for why calcification in untreated HCC is rarely observed can be explained as the following. HCC is less abundant in stromal tissue and has a hypervascular structure, in which blood flow is primarily composed of arterial flow, which is less likely to cause spontaneous microcirculatory disturbance[9-11]. Converse-

Table 1 Summary of 4 cases of hepatocellular carcinoma with ring calcification

Case	No.	Age	Sex	Symptom	AFP (ng/mL)	Size of calcified lesion (cm)	Location	Early enhancement in dynamic CT	Viral infection	Background liver	Histology	Treatment
Fukuya *et al*[6]	1	72	F	No	178	3.0	S8	No	HCV	CH	Mod diff HCC	Partial hepatectomy
Fukuya *et al*[6]	2	77	F	No	9300	3.0	S8	Yes	HCV	LC	Not obtained	None
Kawada *et al*[7]	3	67	F	Abdominal pain Back pain	Not mentioned	3.7	S4	Yes	HCV	CH	Mod diff HCC	Left lobectomy
Our case	4	68	F	No	128	1.0	S4	No	HCV	CH	Poorly diff HCC	Left medial sectionectomy

AFP: Alpha-fetoprotein; CT: Computed tomography; F: Female; S8: Segment 8 (defined by the Couinaud's nomenclature for liver segmentation); S4: Segment 4; HCV: Hepatitis C virus; CH: Chronic hepatitis; LC: Liver cirrhosis; Mod diff: Moderately differentiated; Poorly diff: Poorly differentiated; HCC: Hepatocellular carcinoma.

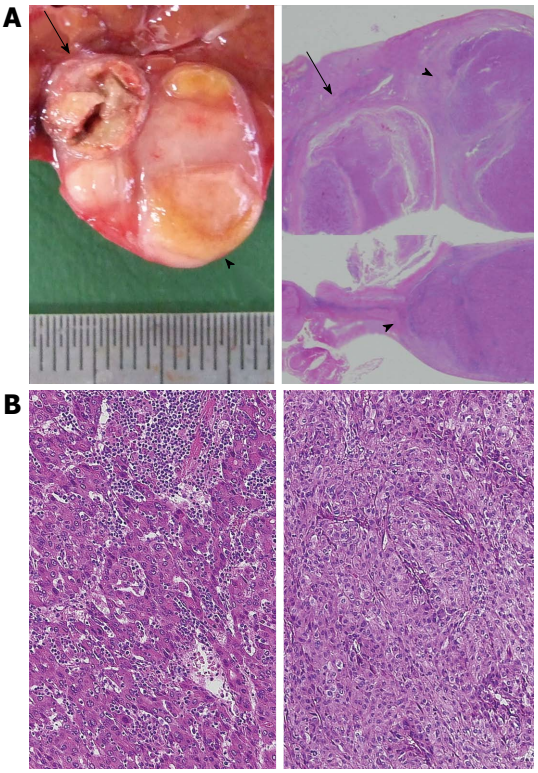

Figure 2 Macroscopic findings of the resected specimen, calcified and non-calcified lesions. A: Left, macroscopic examination showed a 10-mm tumor with ring calcification (arrow) and an 18-mm tumor (arrowhead) existing side-by-side and encapsulated within the same thick fibrous tissue; Right, a prepared specimen (loupe image, hematoxylin and eosin staining); B: Left, microscopic examination findings of the calcified lesion showed the poorly differentiated hepatocellular carcinoma (hematoxylin and eosin staining; original magnification, × 200); Right, microscopic examination findings of the non-calcified lesion showed moderately differentiated hepatocellular carcinoma (hematoxylin and eosin staining; original magnification, × 200).

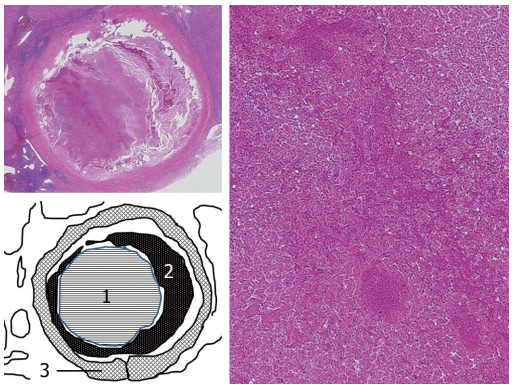

Figure 3 Schematic image of the structure of the calcified lesion. Upper left, loupe image of the calcified lesion (hematoxylin and eosin staining; original magnification, × 5); Right, microscopic findings of the calcified lesion showed that necrotic area was extensively observed in the tumor (hematoxylin and eosin staining; original magnification, × 40); Lower left, schematic of the structure of the calcified lesion. A poorly differentiated tumor, in which spotty necrosis and hemorrhagic necrosis were extensively observed, was surrounded by a fibrous capsule. Calcification was identified between the tumor and the fibrous capsule (1: Poorly differentiated tumor; 2: Calcification; 3: Fibrous capsule).

ly, calcification being observed often in HCC treated by trans-catheter arterial chemoembolization, which causes ischemic necrosis in tumors[4-7], suggests that extensive ischemic necrosis is essential for forming identifiable calcifications in neoplasms.

In the present study, tumors showing a ring calcification with histological findings revealed extensive necrosis histologically. A ring calcification formed in the marginal zone of relatively small tumors in contact with a thick fibrous capsule. Furthermore, these tumors consisted of a single relatively low-differentiation component. In fact, calcified lesions in the previously reported cases were composed of only a moderately differentiated component, whereas the calcified lesion in our case was only composed of a poorly differentiated component; all 3 tumors with histological findings showed poor differentiation for their sizes (1-3.7 cm)[6,7]. Furthermore, these tumors showed no early enhancement in dynamic CT study[6,7], suggesting that these tumors had less abundant arterial blood flow, unlike the usual cases of moderately or poorly differentiated HCC[9-11]. Furthermore, all 3 tumors had a thick fibrous capsule for their size. A fibrous capsule surrounding HCC is usually observed with relatively large and less histologically differentiated tumors[12-14]. It is not known exactly how the fibrous capsule is formed, but the formation is known to result from the interaction between the tumor and host liver and interferes with the growth and invasion of HCC[12-14]. The fibrous capsule is primarily composed of collagenous tissue produced principally

by stellate cells (the so-called fat-storing cell of Ito), which are present among the tumor cells in the vicinity of the boundary between the HCC and non-tumor liver[12-14]. Furthermore, it was reported that the fibrous capsule of HCC contains smooth muscle cells and has contractile ability, whereas the septa of multi-nodular HCC or hepatic cirrhosis does not have either[12]. Based on these findings, we hypothesize that ring calcification forms through the following process. Tumors with ring calcification in this series had less abundant arterial blood flow and had a high internal pressure induced by either the thick fibrous capsule or vigorous proliferation, as suggested by their low differentiation for their sizes. This imbalance between the blood flow and the internal pressure causes a circulatory disturbance in the tumor, resulting in extensive ischemic necrosis. Necrotic tumor cells cause mineral deposition that subsequently involves adjacent collagenous fibers produced by the stellate cell in the marginal zone and elastic fibers derived from the cytoskeleton of degenerated or necrotized tumor cells as the nidi to extend along the fibrous capsule, forming annular calcification. Identifiable calcification cannot be formed in the inner zone because of the absence of collagenous fiber as the nidus. In other words, the prerequisites for forming a ring calcification in untreated HCC are the following: small size, poor differentiation, a thick fibrous capsule, and less abundant arterial blood flow. These prerequisites are the reasons why a ring calcification in untreated HCC is extremely rare. On the other hand, tumors with ring calcification are considered to be likely to show poor differentiation for their sizes. Therefore, HCCs with ring calcification are likely to show a poorer prognosis than other tumors of their size when local ablation therapy is applied for treatment[15]. In treating these lesions, therefore, hepatic resection should be selected even if the size is small and ablation therapy seems feasible[15].

In conclusion, we present an extremely rare case of small HCC (1 cm in diameter) showing ring calcification and a review of the English-language literature including 3 other cases. We believe that ring calcification in untreated HCC is suggestive of the poorer differentiation of the tumors. Therefore, hepatic resection should be performed for these lesions because poor differentiation is considered to be one of the risk factors for recurrence after local ablation therapy.

REFERENCES

1 **Patton RB**, Horn RC. Primary liver carcinoma. Autopsy study of 60 cases. *Cancer* 1964; **17**: 757-768 [PMID: 14176989 DOI: 10.1002/1097-0142]

2 **Maeda M**, Kanayama M, Uchida T, Hasumura Y, Takeuchi J. A case of hepatocellular carcinoma associated with ossification. A case report. *Cancer* 1986; **57**: 134-137 [PMID: 3000570]

3 **Chin NW**, Chapman I, Coopersmith H, Jimenez FA. Parenchymal calcification in hepatocellular carcinoma. *N Y State J Med* 1986; **86**: 596-598 [PMID: 3025789]

4 **Moenandar IM**. Extensive calcification in the stroma of a primary hepatic carcinoma. *J Pathol* 1974; **114**: 53-54 [PMID: 4373560 DOI: 10.1002/path.1711140110]

5 **Teefey SA**, Stephens DH, Weiland LH. Calcification in hepatocellular carcinoma: not always an indication of fibrolamellar histology. *AJR Am J Roentgenol* 1987; **149**: 1173-1174 [PMID: 2825493]

6 **Fukuya T**, Yabuuchi H, Seo Y, Fukuda T, Koga M. Hepatocellular carcinoma with ring calcification: report of two cases. *Radiat Med* 1999; **17**: 379-382 [PMID: 10593291]

7 **Kawada N**, Murata M, Nakayama T, Yukawa M, Okajima K, Ohta Y, Kudo M, Inoue M. Unusual hepatocellular carcinoma with macroscopic biliary tumor thrombus accompanied by rim calcification and no arterial-phase enhancement. *Acta Med Kinki Univ* 2008; **33**: 59-63

8 **Das DK**. Psammoma body: a product of dystrophic calcification or of a biologically active process that aims at limiting the growth and spread of tumor? *Diagn Cytopathol* 2009; **37**: 534-541 [PMID: 19373908 DOI: 10.1002/dc.21081]

9 **Enzan H**, Himeno H, Iwamura S, Onishi S, Saibara T, Yamamoto Y, Hara H. Alpha-smooth muscle actin-positive perisinusoidal stromal cells in human hepatocellular carcinoma. *Hepatology* 1994; **19**: 895-903 [PMID: 8138263 DOI: 10.1002/hep.1840190415]

10 **Maeda T**, Adachi E, Kajiyama K, Takenaka K, Honda H, Sugimachi K, Tsuneyoshi M. CD34 expression in endothelial cells of small hepatocellular carcinoma: its correlation with tumour progression and angiographic findings. *J Gastroenterol Hepatol* 1995; **10**: 650-654 [PMID: 8580408 DOI: 10.1111/j.1440-1746.1995.tb01365.x]

11 **Kimura H**, Nakajima T, Kagawa K, Deguchi T, Kakusui M, Katagishi T, Okanoue T, Kashima K, Ashihara T. Angiogenesis in hepatocellular carcinoma as evaluated by CD34 immunohistochemistry. *Liver* 1998; **18**: 14-19 [PMID: 9548262 DOI: 10.1111/j.1600-0676.1998.tb00121.x]

12 **Kojima A**, Kaneda K, Ueda M, Maki A, Takabayashi A, Fukushima S, Sakurai M, Nagai R, Matsui-Yuasa I. Induction of smooth muscle cells in the fibrous capsule of human hepatocellular carcinoma but not in the septa of hepatic cirrhosis. *Virchows Arch* 1999; **434**: 413-422 [PMID: 10389624 DOI: 10.1007/s004280050360]

13 **Ishizaki M**, Ashida K, Higashi T, Nakatsukasa H, Kaneyoshi T, Fujiwara K, Nouso K, Kobayashi Y, Uemura M, Nakamura S, Tsuji T. The formation of capsule and septum in human hepatocellular carcinoma. *Virchows Arch* 2001; **438**: 574-580 [PMID: 11469689 DOI: 10.1007/s004280000391]

14 **Iguchi T**, Aishima S, Sanefuji K, Fujita N, Sugimachi K, Gion T, Taketomi A, Shirabe K, Maehara Y, Tsuneyoshi M. Both fibrous capsule formation and extracapsular penetration are powerful predictors of poor survival in human hepatocellular carcinoma: a histological assessment of 365 patients in Japan. *Ann Surg Oncol* 2009; **16**: 2539-2546 [PMID: 19533247 DOI: 10.1245/s10434-009-0453-1]

15 **Huang J**, Yan L, Cheng Z, Wu H, Du L, Wang J, Xu Y, Zeng Y. A randomized trial comparing radiofrequency ablation and surgical resection for HCC conforming to the Milan criteria. *Ann Surg* 2010; **252**: 903-912 [PMID: 21107100 DOI: 10.1097/SLA.0b013e3181efc656]

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