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Giant hepatocellular carcinoma with bone metastasis in a young adult, emerged from pigmented adenoma with beta-Catenin activation: A case report



Sebastian Lünse^{a,*}, Paula Döring^b, Claus-Dieter Heidecke^a, Lars Ivo Partecke^a

^a Department of General Surgery, Visceral, Thoracic and Vascular Surgery, Universitätsmedizin Greifswald, Germany

^b Institute of Pathology, Universitätsmedizin Greifswald, Germany

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ABSTRACT

INTRODUCTION: Hepatocellular carcinomas (HCC) that are very large in size are a very rare finding in young adult. The malignant transformation of a pigmented hepatocellular adenoma (HCA) with beta-Catenin activation is a possible cause for appearance of HCC.

PRESENTATION OF CASE: We present the case of a 33-year-old male with a huge HCC with bone metastasis, emerged from pigmented HCA with beta-Catenin activation. As a two-stage surgical procedure, a left hepatectomy followed by a partial rib resection was performed.

DISCUSSION: Giant hepatocellular carcinomas mostly develop in non-cirrhotic livers and at time of diagnosis an extrahepatic spread occurs in up to 15%. In the present case, the progression from a benign HCA to malignant HCC was documented, as a unique finding. Surgical resection is the only curative treatment and was successfully performed in this case.

CONCLUSION: Hepatobiliary surgery with resection of metastases is the treatment with best long-term survival for patients with huge HCC. Molecular characterization as well as pigmentation analysis is useful tools for risk assessment of HCA.

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1. Introduction

The present work has been reported in line with the SCARE criteria [1].

Hepatocellular carcinoma (HCC) is the most common primary malignant tumor of the liver and the second leading cause of cancer-related death in the world [2]. Almost 80% of HCC cases are associated with cirrhosis due to chronic hepatitis B or C virus infection [3]. However, HCCs that are very large in size and mass mostly develop in non-cirrhotic livers [4]. Surgical resection is the only potentially curative treatment for patients with adequate liver functional reserve. We present the case of a patient with an extensive HCC, who clinically presented with thoracic pain due to an extrahepatic metastasis.

2. Presentation of case

2.1. Anamnesis and preoperative evaluation

A 33-year-old male presented to an ambulant orthopedic surgeon with left thoracic pain for six months. The patient's history offered no trauma, no alcoholism or smoking as well as no drug abuse or intake of steroid hormones. Clinical examination revealed selective pressure pain over the fifth rib near the left mammilla. As an incidental finding, a painless abdominal distension was seen. Ultrasound showed a solid tumor, which filled the entire abdomen. A gadoteric acid-enhanced MRI was performed and revealed a giant inhomogeneous tumor originating from the left liver lobe with compression of surrounding organs (Fig. 1A). Liver biopsy revealed a hepatocellular adenoma (HCA) with conspicuous cytoplasmic yellow-brown granular pigments (Fig. 4, upper line). Tumor cells showed nuclear β -Catenin expression and over-expression of glutamine synthetase, leading to the diagnosis of HCA with β -Catenin activation. Although in biopsy tissue transition to HCC was not evident, progression to HCC was suspected due to the big tumor size. Furthermore, a single-photon emission computed tomography (SPECT) showed suspect tumor in the left fifth rib (Fig. 1B), and a CT-guided puncture revealed HCC metastasis, verifying the suspicion of malignant progression. A moderate

* Corresponding author at: Department of General Surgery, Visceral, Thoracic and Vascular Surgery, Universitätsmedizin Greifswald, Ferdinand-Sauerbruch-Straße, 17475 Greifswald, Germany.

E-mail addresses: sebastian.luense@uni-greifswald.de (S. Lünse), paula.doering@uni-greifswald.de (P. Döring), heidecke@uni-greifswald.de (C.-D. Heidecke), partecke@uni-greifswald.de (L.I. Partecke).

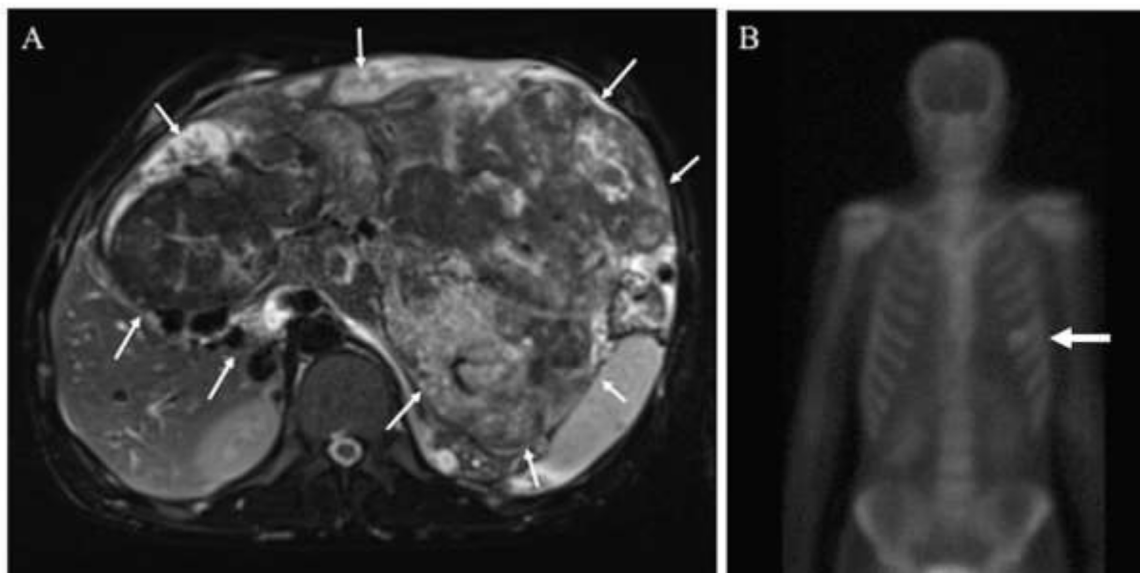


Fig. 1. (A) Gadoxetic acid-enhanced MRI axial T2-weighted showed large inhomogeneous abdominal mass and continuation with the parenchyma of left hepatic lobe (arrows). (B) Single-photon emission computed tomography (SPECT) showed metastasis of fifth left rib (arrow).



Fig. 2. (A) In situ appearance of the hepatocellular carcinoma mass. (B) Image of intraoperative situs after left hemihepatectomy showed prominent feeding vessel originating from the left gastric artery (arrow).

increase of transaminases with alanine aminotransferase (ALT) of $0.92 \mu\text{katal/l}$ (normal: $0.22\text{--}0.77$) and aspartate aminotransferase (AST) of $1.0 \mu\text{katal/l}$ (normal: <0.59) was assessed by blood sample. The tumor markers alpha-fetoprotein (AFP), cancer embryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) were all within normal limits, whereas carbohydrate antigen 125 (CA125) was moderately increased with 24.8 U/ml (normal: <20). There was no evidence of hepatitis B or C virus infection. The liver function was normal as measured by ICG (indocyanine green)-PULSION. Preoperative CT volumetric measurement revealed a right liver lobe volume of 1367 cubic centimeter by using the summation-of-area method.

2.2. Two-stage surgical procedure

A left hepatectomy including liver segment one was performed under general anaesthesia. The huge tumor did not invade surrounding organs and hepatic cirrhosis or peritoneal metastasis was not observed (Fig. 2A). The intraoperative ultrasound revealed no intrahepatic metastases. After cholecystectomy and complete

mobilization of the left liver, the left portal vein and left hepatic artery were ligated and divided. Liver transection of left liver including segment I and partial segment IV was performed by using Endo GIA™ 60-mm vascular with Tri-Staple™ Technology (Covidien, Mansfield, Massachusetts, USA), whereas larger vessels and biliary tracts were overstitched (Fig. 2B). The resection surface was sealed with fibrin sealant patch (TachoSil®, Takeda, Osaka, Japan) to avoid bleeding. The intraoperative course was uneventful, the tumor capsule was not disrupted and there was no need of blood transfusion. The giant tumor mass was found to be $34 \times 24 \times 24 \text{ cm}$ in size and 7.2 kg in weight. Macroscopic examination showed a multinodular and multicoloured tumor with yellow-green as well as dark pigmented areas (Fig. 3A and B). Histological evaluation revealed a well-differentiated HCC with trabecular growth pattern, invasion of portal vein branches and tumor-free resection margins. Interestingly, tumor cells showed regularly membranous expression of β -Catenin (Fig. 4, lower line). Tumor cells of the macroscopically dark coloured areas in histology contained brown

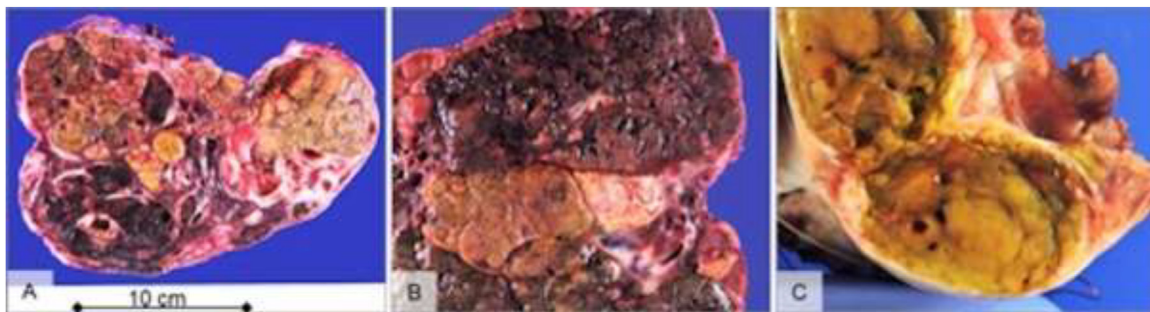


Fig. 3. (A, B) Multinodular and multicoloured appearance of the tumor with yellow-green areas, caused by bile production, and dark pigmented areas. (C) Yellow-green appearance of the bone metastasis due to bile deposition.

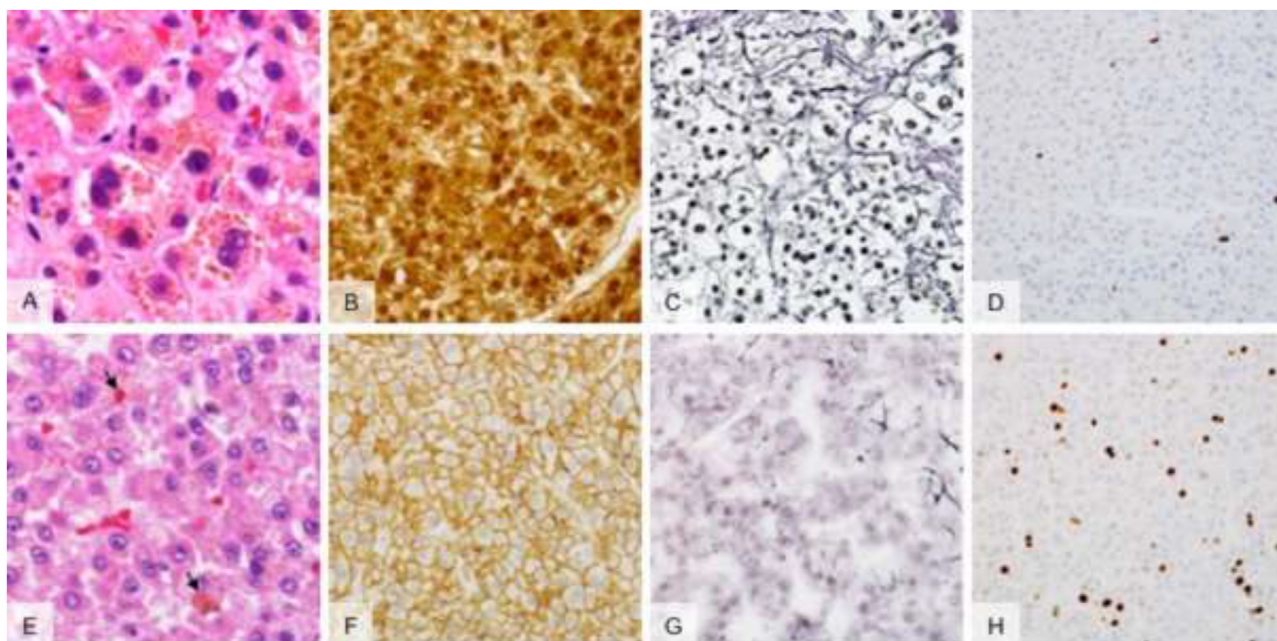


Fig. 4. Upper line: (A) Hepatocellular adenoma with cytoplasmic granular pigments, (B) nuclear β -Catenin expression, (C) conserved reticulin fiber meshwork and (D) very low proliferative activity. Lower line: (E) Hepatocellular carcinoma with trabecular growth pattern, low nuclear atypia and bile plugs (arrows), (F) showing regular membranous β -Catenin expression, (G) fiber-destructive growth and (H) medium proliferative activity. A, E: hematoxylin & eosin; B, F: β -Catenin immunohistochemistry; C, G: Gomori silver staining; D, H: Ki67 immunohistochemistry.

cytoplasmic pigments (data not shown), just as observed in the cells of the HCA. As a two-stage surgical procedure, partial en bloc resection of the left fifth rib was performed 4 weeks after hepatectomy. The defect of the thoracic wall was repaired by using Peri-Guard® Repair Patch (Synovis Life Technologies, Saint Paul, Minnesota, USA), a biological tissue prepared from bovine pericardium. In summary, this case was classified as a pT3a pN0 pM1 Stage IV, according to the 7th edition of the UICC TNM staging system for HCC.

The post-operative period was uneventful and the patient was discharged home one week after the second operation. A follow-up surveillance according to the recent guidelines of the European Association for the Study of the Liver (EASL) was initiated.

3. Discussion

Giant hepatocellular carcinomas have a diameter over 10 cm, whereas a diameter over 20 cm is extremely rare [5]. Interestingly, very large HCCs mostly develop in non-cirrhotic livers [4]. At time of diagnosis an extrahepatic spread occurs in only about 5–15% of

patients and mainly in advanced-stage primary tumors over 5 cm [6]. The most common sites of HCC metastases are lung (49%), abdominal organs (24%) and bone (13–16%). Skeletal metastases appear as expansive soft tissue masses with bone destruction and mainly involved sites are the vertebrae, pelvis, ribs, skull, humerus and sternum [7].

In the presented case the progression from a HCA with β -Catenin activation to HCC was documented. Molecular characterization of HCAs has been practiced for few years now, resulting in an improved risk stratification of the heterogeneous entity of HCAs [8]. 10–15% of HCAs show an activating mutation of β -Catenin with nuclear translocation. These β -Catenin activated HCAs are often associated with male sex and administration of androgenic hormones and have an increased risk of malignant transformation [9]. In this case the patient negated taking of steroid hormones. An interesting histological finding was a pigmentation of the HCA. It is suggested that these pigments constitute lipofuscin deposits and several reports indicate an increased risk of malignancy in pigmented HCAs [10,11]. The pigments were also found in the HCC cells, but, unexpectedly, the nuclear β -Catenin activation of the

HCA was not preserved in the HCC cells. However, pigmentation of HCAs besides molecular characterization could serve as additional hint in evaluation of malignant potential of HCAs.

Currently, surgical resection is the only curative treatment with the best long-term survival [12]. Preoperative liver function as a key parameter and the skill and experience of the surgeon significantly affect the success of resection in complicated HCC [13]. Recurrence is the major challenge, as it occurs in approximately 70% of patients within 5 years after hepatic resection [14]. Predictive factors of recurrence are disruption of tumor capsule, daughter nodules, positive surgical resection margins and blood transfusion [15].

According to the literature, we recommend a therapy specific to the patient on a case-by-case basis [16]. To our knowledge, this is the first case report of a two-staged surgical resection of a giant HCC with skeletal metastasis in a young adult.

4. Conclusion

Bone metastasis of a hepatocellular carcinoma (HCC) is a very rare cause of thoracic pain. However, it should be considered as a possible differential diagnosis. Hepatocellular adenomas (HCA) with an activating mutation of β -Catenin, which occurs in up to 15% of cases, have a high risk of malignant transformation. Molecular characterization and morphological feature of pigmentation are useful tools for risk assessment of HCAs and should be performed. Hepatobiliary surgery with metastasis resection is the only curative treatment and can be safe and effective even in patients with giant HCCs, as our case report shows.

Conflicts of interest

None.

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Ethical approval

Not applicable.

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.

Author contributions

Sebastian Lünse: study concept, data collection, literature research and writing the manuscript.

Paula Döring: data collection, literature research and writing the manuscript.

Sebastian Lünse and Paula Döring contributed equally to this work.

Claus-Dieter Heidecke: editing and supervision of this paper.

Lars Ivo Partecke: editing and supervision of this paper.

Guarantor

Sebastian Lünse.

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