



Contents lists available at ScienceDirect

International Journal of Surgery Case Reports

journal homepage: www.casereports.com

Undifferentiated carcinoma of the liver in a 3-year-old girl treated by neoadjuvant chemotherapy and complete resection

Takanori Ochi^{a,*}, Junya Fujimura^b, Atsushi Arakawa^c, Geoffrey J. Lane^a, Atsuyuki Yamataka^a, Akio Saiura^d^a Department of Pediatric General and Urogenital Surgery, Juntendo University School of Medicine, 2-1-1 Hongo, Bunkyo-ku, 113-8421, Tokyo, Japan^b Department of Pediatrics and Adolescent Medicine, Juntendo University School of Medicine, 2-1-1 Hongo, Bunkyo-ku, 113-8421, Tokyo, Japan^c Department of Human Pathology, Juntendo University School of Medicine, 2-1-1 Hongo, Bunkyo-ku, 113-8421, Tokyo, Japan^d Department of Hepatobiliary Pancreatic Surgery, Juntendo University School of Medicine, 2-1-1 Hongo, Bunkyo-ku, 113-8421, Tokyo, Japan

ARTICLE INFO

Article history:

Received 26 November 2020

Accepted 30 November 2020

Available online 2 December 2020

Keywords:

Undifferentiated carcinoma

Liver

Children

Neoadjuvant chemotherapy

Case report

ABSTRACT

INTRODUCTION: Undifferentiated carcinoma (UC) of the liver has only been reported in three adults in the English language literature and is so rare it has never been reported in a child. Our management is presented to improve knowledge of its treatment.

CASE PRESENTATION: A 3-year-old previously well Japanese girl was referred for further assessment/management of an abdominal mass. On examination an obvious right hypocostal mass was visible extending across the midline. Diagnostic imaging identified a 12.5 cm mass on the ventral surface of the liver containing multiple cystic lesions extending along Glisson's capsule with invasion to the portal vein. Open biopsy eventually led to a diagnosis of poorly differentiated or UC of the liver with embryonal features. Resection of hepatic segments 4b and 5 after a remarkable initial response to cisplatin/doxorubicin that shrank the tumor substantially, separating it from Glisson's capsule enabled total excision. Surgery was successful and tolerated well with unremarkable postoperative recovery. Unfortunately, ascites due to peritoneal carcinomatosis developed 4 months postoperatively and she died 5 months later.

CONCLUSION: The initial impressive response to neoadjuvant chemotherapy and successful surgery was unexpectedly fortuitous but inadequate for controlling such an aggressive malignancy. Our case demonstrates the value of neoadjuvant chemotherapy.

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1. Introduction

Undifferentiated carcinoma (UC) of the liver is an extremely rare, aggressively malignant condition reported in only 3 adults in the English literature [1–3]. Nakasuka et al. [1] reported a case with neuroendocrine features characterised by high serum neuron-specific enolase (NSE) that responded well to etoposide + cisplatin (CDDP) with NSE decreasing to normal. Maeda et al. [2] reported a case of fatal acute intra-abdominal haemorrhage from a ruptured liver, that was found to be caused by UC of the liver with diffuse proliferation of anaplastic cells positive for NSE suggesting neuroendocrine differentiation at autopsy; and Hiraki et al. [3]

reported a case who had a mass with cystic and partially solid components located in segments 6 and 7 of the liver removed successfully by radical surgery alone, without neoadjuvant or adjuvant chemotherapy, who is well, with no evidence of recurrence some three years postoperatively. Due to its rarity, the natural history (typical mode of presentation, routine investigations, and histopathologic/biologic characteristics) of UC of the liver and management strategies have not been established. To the best of our knowledge this is the first report of UC of the liver in a child.

2. Presentation of case

A previously well 3-year-old Japanese girl of average height and weight was referred to our hospital for further management of an abdominal mass. She had no drug history and no relevant family history. No patient perspective was possible given the age of our case.

On examination at presentation, there was an obvious right hypocostal mass that extended across the midline. She was admitted and blood biochemistry and diagnostic radiology investigations were ordered to obtain basic information about the mass. Serum

Abbreviations: UC, undifferentiated carcinoma; HB, hepatoblastoma; CDDP, cisplatin; DOX, doxorubicin; LTx, liver transplantation; PRETEXT, pretreatment extent of disease; POSTEXT, post-treatment extent of disease.

* Corresponding author.

E-mail addresses: tochi@juntendo.ac.jp (T. Ochi), junya-f@juntendo.ac.jp (J. Fujimura), aatsushi@juntendo.ac.jp (A. Arakawa), geoffrey@juntendo.ac.jp (G.J. Lane), yama@juntendo.ac.jp (A. Yamataka), a-saiura@juntendo.ac.jp (A. Saiura).

<https://doi.org/10.1016/j.ijscr.2020.11.153>

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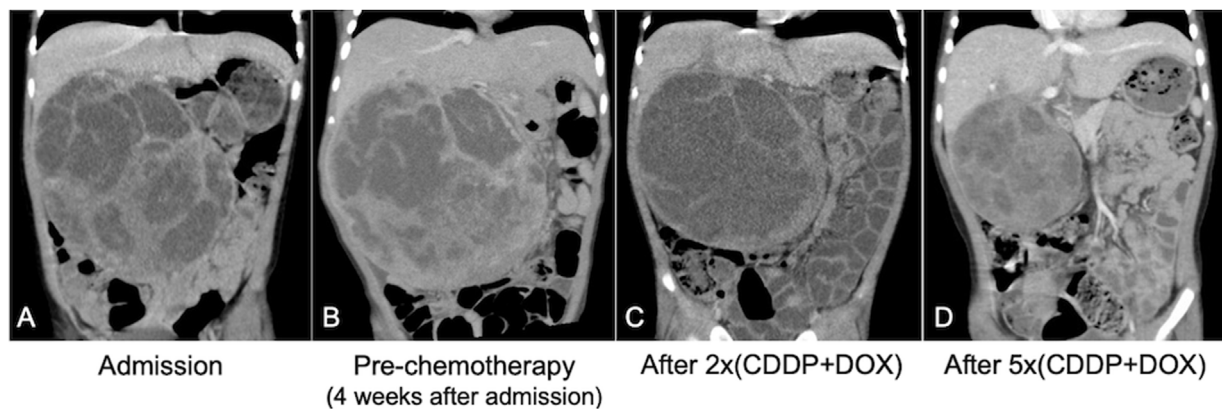


Fig. 1. Change in tumor size after neoadjuvant chemotherapy.

A. Computed tomography (CT) scan on admission. The tumor is on the ventral surface of the liver containing multiple cystic lesions with ring enhancement, extending along Glisson's capsule with invasion to the portal vein.

B. CT scan 4 weeks after admission; pre-chemotherapy.

C. CT scan 8 weeks after admission; after 2 cycles of CDDP + DOX.

D. CT scan 16 weeks after admission; after 5 cycles of CDDP + DOX. The tumor has shrunk remarkably separating from Glisson's capsule.

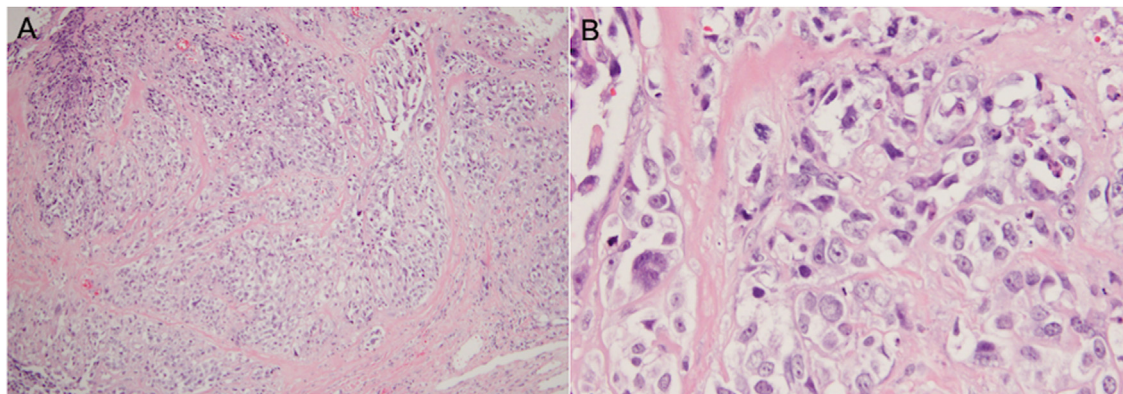


Fig. 2. Histopathology of open liver (tumor) biopsies.

Micrographs of open liver (tumor) biopsy (A: HE x12.5; B: HE x400) showing diffuse infiltration of tumor cells with nuclear pleomorphism.

lactate dehydrogenase was elevated (LDH; 1,339 IU/L) and while specific serum tumor markers such as NSE (224 ng/mL), soluble interleukin-2 receptor (sIL-2R; 982 IU/mL), CA125 (315 IU/mL), CA19-9 (51 IU/mL), and PIVKA-II (84mAU/mL) were elevated, alpha-fetoprotein (AFP; 4 ng/mL) and CEA (1.5 ng/dL) were normal. Computed tomography (CT) confirmed a mass, 12.5 cm in maximum diameter, located on the ventral surface of the liver containing multiple cystic lesions with ring enhancement, extending along Glisson's capsule with invasion to the portal vein (Fig. 1A).

Open biopsy of the mass was performed two days after admission to avoid complications of needle biopsy such as bleeding. Microscopic sections of biopsy specimens showed diffuse infiltration of tumor cells with nuclear pleomorphism and cohesiveness (Fig. 2A and B) with no specific structure or differentiation. Immunohistochemistry was positive for epithelial markers (pan cytokeratin (CK) antibodies AE1/AE3, CK19, CK7), vimentin, SALL4, Glypican3, CD10 and p53, while negative for CK20, EMA, CD30, AFP, HCG- β , HepPar1, D2-40, CDX2, β -catenin and p40. A definitive diagnosis could not be made, but a germ cell tumor or carcinoma with germ cell differentiation was suspected because SALL4 and Glypican3 were both positive. Biopsy specimens were sent for Central Pathology Review by paediatric tumor pathology specialists. Additional immunostaining was performed with SMARCB1, SMARCA2, SMARCA4, ARID1A, and LIN28 being positive and Oct3/4, CD117, DLK1, and vimentin being negative, a reflection of how poorly differentiated the tumor was. Their diagnosis, which took

almost a month to be finalised, was poorly differentiated or UC of the liver with embryonal features.

During this time, the tumor had grown to 14.5 cm in maximum diameter (Fig. 1B) with enlargement of multiple mediastinal lymph nodes. Gallium scintigraphy was positive for the liver tumor and the mediastinum. Preoperative liver CT volumetry [4] indicated that the standard liver volume would be less than 20% following surgical resection, a level consistent with high postoperative morbidity and liver failure [5]. Thus, her tumor was group III [6] using the pretreatment extent of disease (PRETEXT) system for classifying primary hepatic malignancies in children, which meant that the tumor was inoperable and that she was also not a viable candidate for primary liver transplantation (LTx).

In the absence of guidelines for the treatment of UC of the liver, we referred to treatment options for hepatoblastoma (HB) and commenced neoadjuvant chemotherapy with cisplatin/doxorubicin (CDDP + DOX) [7,8] starting with one dose of CDDP (4.0 mg/kg/dose) and two doses of DOX (2.0 mg/kg/dose). The response was immediate and impressive. A further four cycles of one dose of CDDP (5.2 mg/kg/dose) and two doses of DOX (2.6 mg/kg/dose) followed by one dose of CDDP (5.2 mg/kg/dose) without DOX to prevent DOX-induced cardiomyopathy shrank the tumor so remarkably (Fig. 1C and D) that it separated from Glisson's capsule to become a post-treatment extent of disease (POSTEXT) II [6] tumor that was excised completely by open resection of segments 4b and 5 performed by a team comprised of two board-

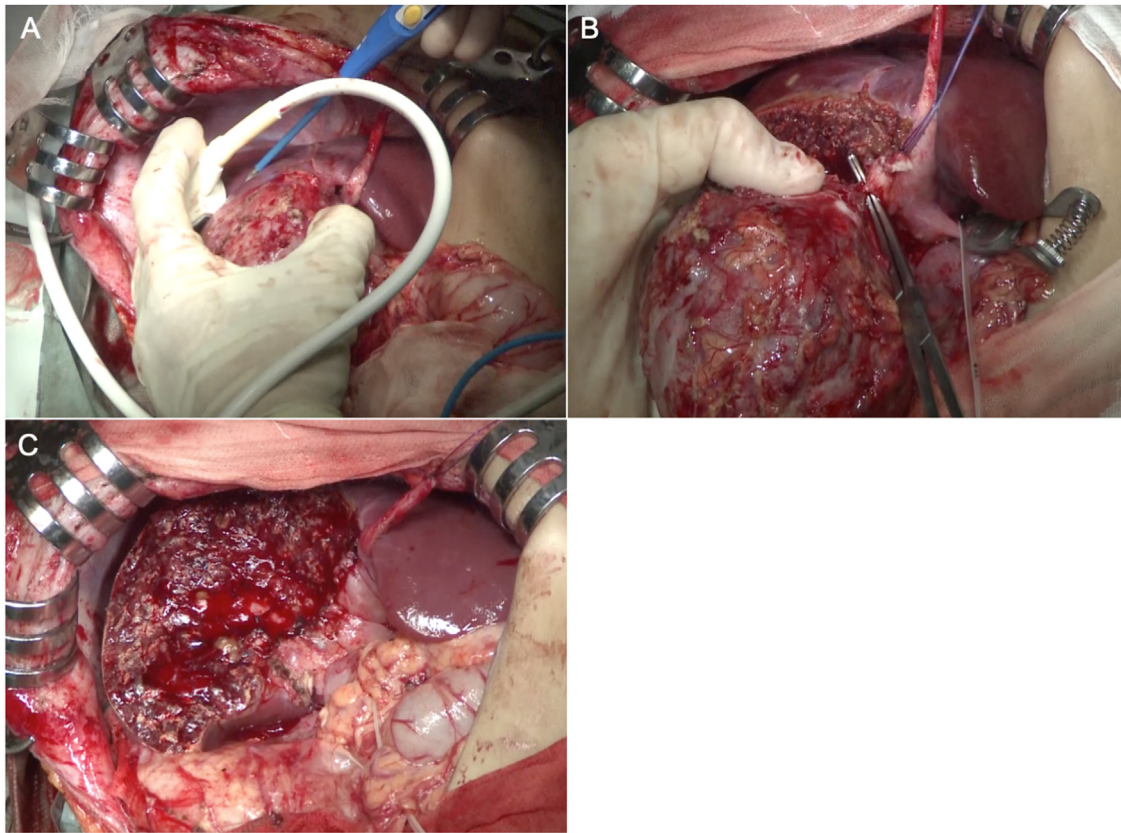


Fig. 3. Operative findings.

Intraoperative ultrasound was used to confirm the relationship of the tumor to vascular structures, and guide dissection for resection (A). The Pringle maneuver was used during transection (B), and tumor was excised completely by resecting segments 4b and 5 (C).

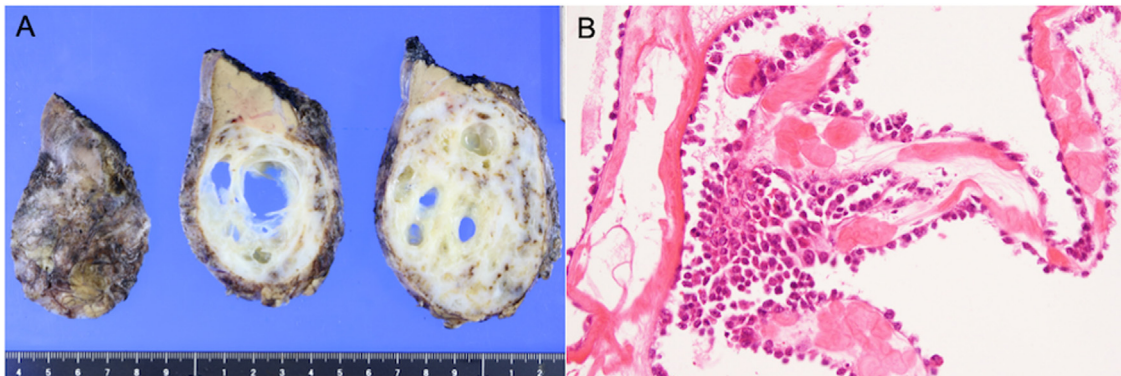


Fig. 4. Histopathology of resected specimens.

Macroscopic appearance (A) and micrographs (B: HE x200) of the resected specimen showing cysts lined by tumor cells with focal papillary projections.

certified paediatric surgeons, one with 34 years' experience (AY) and one with 11 years' experience (TO) and one board certified adult hepatobiliary pancreatic surgeon with 26 years' experience for supervisory support (AS). During surgery, ultrasonography was used as shown in Fig. 3A to confirm the relationship of the tumor to vascular structures and guide dissection for resection. The Pringle maneuver was used during transection (Fig. 3B) enabling the tumor to be excised completely (Fig. 3C). Neither mediastinal dissemination nor ascites were noted. No additional procedures were considered. The abdominal cavity was irrigated and there were no signs of bleeding; a drainage tube was not placed. Total operative time was 5 h and 20 min. Blood loss was 60 mL. The patient tolerated surgery well with no perioperative complications and uneventful postoperative recovery. Adjuvant chemotherapy was not indicated.

Histopathology confirmed all surgical margins were negative for malignancy (Fig. 4A). Microscopic sections showed numerous diffuse cystic lesions lined with tumor cells with focal papillary projections into the cystic spaces (Fig. 4B). Scattered necrosis/haemorrhage secondary to neoadjuvant chemotherapy was observed. Immunohistochemical staining was positive for AE1/AE3, SALL4, Glypican3, CD10 and EMA, and negative for AFP, CD30, HCG- β , HepPar1, CDX2 and podoplanin.

Some four months after surgery, she developed ascites secondary to peritoneal carcinomatosis. Unfortunately, her creatinine clearance deteriorated after only two doses of CDDP (5.8 mg/kg/dose). She was discharged with no active treatment plan about one month before she eventually passed away, nine months after surgery.

The work has been reported in line with the Scare 2018 criteria [9].

3. Discussion

Two of the three cases in the literature had neuroendocrine features and were diffuse and one was more solitary and amenable to surgery. Our case had multiple cystic lesions with partial solid components on CT which would categorise her as being of the solitary type, but her tumor was considered inoperable because of extensive spread within the liver and insufficient volume of future liver remnant.

While some studies recommend LTx for HB patients with PRE-TEXT/POSTTEXT groups III and IV, claiming five-year survival rates of 77%–100% [10–12], others recommend extended hepatic resection, also claiming excellent overall survival rates of 80%–88% [13,14]. We do not know if LTx could have prevented metastases or if immunosuppressants would have been problematic, but in hindsight, complete surgical resection may have been too optimistic for such an aggressive tumor because even though neoadjuvant chemotherapy would have weakened the tumor and all resected edges were negative for abnormal histopathology, she succumbed to overwhelming metastases.

4. Conclusion

UC should be included in the provisional diagnosis of a child with a right upper quadrant mass with or without ascites. Its rarity has prevented appropriate chemotherapeutic and surgical strategies from being established, however, our case demonstrates the importance of gross inspection as a clinical skill to identify masses as early as possible and the value of neoadjuvant chemotherapy for facilitating surgical intervention.

Declaration of Competing Interest

The authors report no declarations of interest.

Funding

None.

Ethical approval

This case report was approved by the Ethics Committee of Juntendo University School of Medicine (approval number: JHS20-010).

Consent

Written informed consent was obtained from the patient's parents for preparation and publication of this case report and accompanying images.

There is no identifying characteristics in the manuscript.

Author contribution

Akio Saiura, Atsuyuki Yamataka, and Takanori Ochi performed surgery on our patient. Takanori Ochi wrote the manuscript

with help from Junya Fujimura and Atsushi Arakawa. Geoffrey J. Lane, Atsuyuki Yamataka, and Akio Saiura edited and revised the manuscript and prepared it for submission.

Registration of research studies

Not applicable.

Guarantor

The Guarantor of this case report is Takanori Ochi (Associate Professor of the Department of Pediatric General and Urogenital Surgery, Juntendo University School of Medicine).

Acknowledgements

We wish to express our appreciation to Eri Abe, Yuichiro Miyake, and Osamu Tomita for their contributions and commitment to the care of our patient and Shiho Yoshida, Hiroyuki Koga, and Toshiaki Shimizu for their support and encouragement in preparing this report.

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