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Case report

Peritoneal hepatoid carcinoma with chemotherapy response and possible stem cell involvement

Christine K.C. Loo[a], Suzanne Danieletto[b], Michael Friedlander[c], Michael A. Pearen[d], Grant A. Ramm[d,e,*]

[a] Department of Anatomical Pathology, NSW Health Pathology, Prince of Wales Hospital, Randwick, NSW 2031, Australia
[b] Douglass Hanly Moir Pathology, Macquarie Park, Sydney, NSW, Australia
[c] Department of Medical Oncology, Prince of Wales Hospital, Randwick, NSW 2031, Australia
[d] Hepatic Fibrosis Group, QIMR Berghofer Medical Research Institute, Brisbane, QLD 4006, Australia
[e] Faculty of Medicine, The University of Queensland, Brisbane, QLD 4006, Australia

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ABSTRACT

Hepatoid carcinoma is a rare type of malignancy showing hepatocellular differentiation, without tumour in the liver. Hepatoid carcinoma in the female genital tract of older patients has been suggested to be a rare type of yolk sac tumour, possibly derived from a somatic tumour. However, the mechanisms causing a somatic tumour to show hepatoid or yolk sac tumour differentiation are unknown. We present a case report of peritoneal hepatoid carcinoma with immunohistochemical evidence of stem cells and hepatic stellate cells in this tumour, which have not been previously reported. We compare morphological features in our case of hepatoid carcinoma with reported findings in hepatoid yolk sac tumour and hepatocellular carcinoma and discuss the possible histogenesis of this tumour and findings suggestive of tumour stroma interactions, using information from our observations and correlating this with results reported from animal experiments, human developmental studies and other reports of hepatoid carcinoma.

1. Introduction

Hepatoid carcinoma is a rare type of extrahepatic adenocarcinoma, expressing alpha fetoprotein and showing morphological resemblance to hepatocellular carcinoma [1]. Hepatoid carcinoma can arise from endodermal and urogenital organs, the stomach being one of the more common sites, with other sites including peritoneum and ovary. We present detailed histological findings in a case of hepatoid carcinoma before and after chemotherapy response, including immunohistochemistry of possible stem cells and specialised stromal cells. The pathogenesis of this tumour is uncertain and we discuss the possible mechanisms for its histogenesis and relationship to hepatoid yolk sac tumour in female genital tract of older patients.

2. Case report

The patient is a 63 year old woman who had just completed radiotherapy for a grade 1, ER and PR positive, HER 2 negative invasive ductal carcinoma of the breast treated initially with a wide local excision. Sentinel lymph node biopsy was negative. She has no family history of malignancy. She presented with nausea, 6 kg weight loss over 4 months, lethargy and diarrhoea. CT scan showed ascites, bilateral pleural effusions and widespread peritoneal and omental tumour deposits. The liver was normal. An omental core biopsy showed widespread invasive carcinoma with hepatoid features (Fig. 1A), with no resemblance to the breast carcinoma removed 9 months earlier. No bile formation was found but canaliculi were demonstrated with polyclonal CEA immunohistochemistry (Fig. 1B). There was patchy expression of alpha fetoprotein (Fig. 1C) and P53 (Fig. 1D), as well as inhibin A and pankeratin antigens in hepatoid tumour cells, and occasional hepatoid cells expressed Her-2 and synaptophysin antigens by the immunoperoxidase method (not shown). SALL 4, oestrogen and progesterone receptor antigens were not expressed in the tumour cells (not shown). Scattered small tumour cells expressed oct 3/4 (Fig. 1E), as well as calretinin, CA125 and keratin 7 antigens (not shown). C-kit immunohistochemistry showed stellate shaped perisinusoidal cells (Fig. 1F). Additional immunohistochemical findings were also consistent with hepatoid carcinoma, with a summary of all immunohistochemistry observations listed in Table 1. Her CA 125 was 1300 and AFP 140,000. CEA, CA19.9, CA 15.3 were all normal. She was

* Corresponding author at: Hepatic Fibrosis, Cell and Molecular Biology, QIMR Berghofer Medical Research Institute, PO Royal Brisbane and Women's Hospital, Brisbane, QLD 4029, Australia.
E-mail address: Grant.Ramm@qimr.edu.au (G.A. Ramm).

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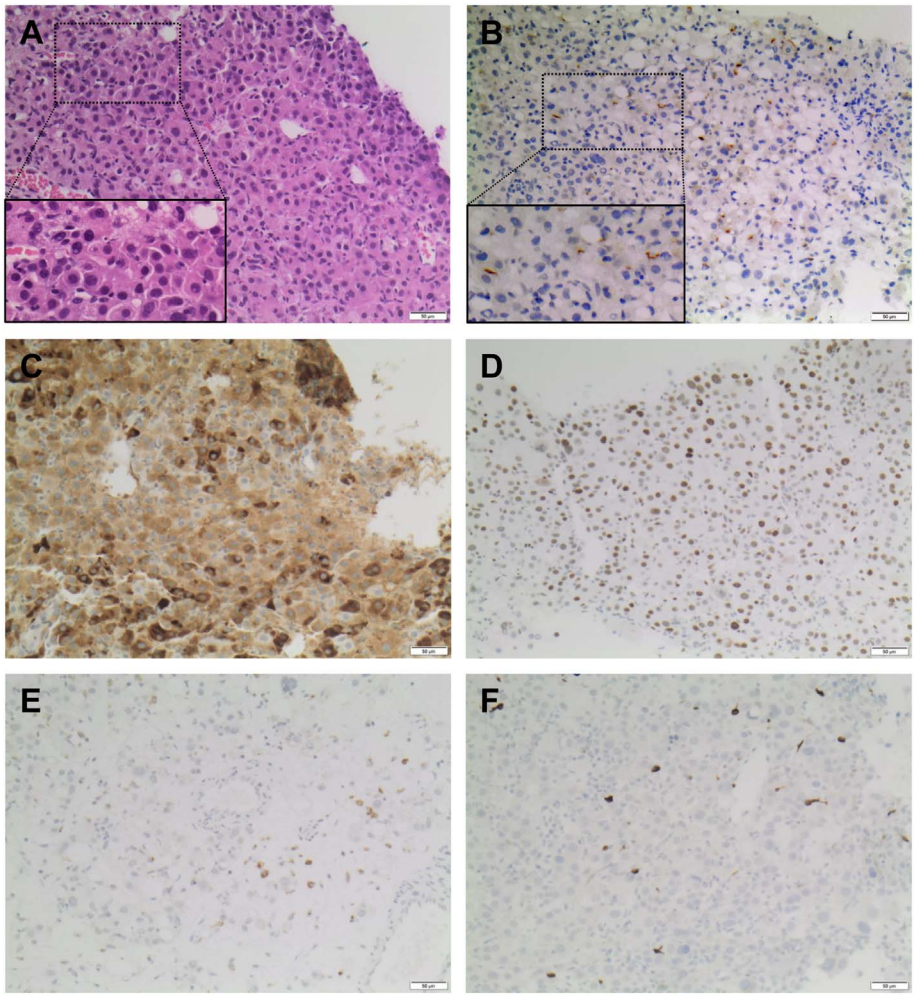

Fig. 1. Pre-treatment omental core biopsy specimen. (A) The tumour showed hepatoid cells with dense eosinophilic cytoplasm and large central nuclei. A few cells appear multinucleated and patchy macrovesicular steatosis is seen. In some areas, sinusoids lined by flattened spindle cells can be seen (H&E stain). (B) The polyclonal CEA immunoperoxidase stain shows a few canalicular structures between the hepatoid tumour cells (inset showing linear pCEA staining between hepatoid cells), in keeping with a diagnosis of hepatoid carcinoma. (C) The alpha fetoprotein immunoperoxidase stain shows variable expression of this antigen in many of the tumour cells. Alpha fetoprotein antigen was not expressed in the post treatment sample (not shown). (D) The P53 immunoperoxidase stain shows nuclear expression of this antigen with varying intensity in many of the tumour cells. P53 antigen was also expressed in tumour cells after treatment (not shown). (E) Oct 3/4 antigen is expressed in scattered small cells with little cytoplasm, while the large hepatoid cells do not express this antigen, by the immunoperoxidase method. Similar findings were seen in the post treatment sample (not shown). (F) C-kit antigen is expressed in scattered small tumour cells and some stellate-shaped cells in the pre-treatment biopsy.

treated with neoadjuvant chemotherapy with cisplatin and etoposide (4 cycles) with a fall in AFP to 1500 and CA 125 to 30. A repeat CT scan confirmed significant resolution of omental and peritoneal disease consistent with a partial response.

Written informed consent for the procedures and studies outlined in this case study was obtained from the patient.

The subsequent specimens obtained at interval debulking showed large nodules of hepatoid carcinoma, on the serosal surface of the uterus, fallopian tubes, ovaries, omentum and scattered throughout the abdominal and pelvic peritoneum. Multiple blocks were taken from each specimen and multiple levels of each tissue block examined to search for other components such as serous carcinoma or yolk sac tumour. The uterus, tubes and ovaries appeared otherwise normal. The tumour had an unusual brown colour. Bile formation was found in some nodules (Fig. 2A), confirmed with a Hall's stain for bilirubin (Fig. 2B). The tumour cells were morphologically similar to the pre-treatment biopsy but appeared larger with more cytoplasmic vacuolation, nuclear pleomorphism and prominent nucleoli (Fig. 2A), multinucleation and areas of necrosis. Alpha-fetoprotein was not expressed in the tumour cells and P53 expression was possibly less than in the pre-treatment biopsy (not shown). Immunohistochemistry was otherwise similar to the pre-treatment core biopsy and all results are either listed in Table 1 or illustrated in Figs. 2 and 3. Moderate to strong expression of arginase was seen in many of the hepatoid cells (Fig. 2C). The c-kit immunoperoxidase stain showed stellate cells and small tumour cells similar to the pre-treatment core biopsy (Fig. 2D). No evidence of yolk sac tumour, teratoma or more common forms of ovarian or peritoneal surface epithelial tumour was found in any of the specimens despite examination of multiple blocks of tissue. Some tumour nodules showed small cysts with similar immunophenotype to the overlying mesothelium, including calretinin, D240, keratin 19 (Fig. 3A) and desmin expression (Fig. 3B), but no portal tracts were identified. Keratin 7 (not shown) and 19 antigens (Fig. 3A) were expressed in some of the smaller tumour cells but not in the large hepatoid tumour cells. In some areas, there were stellate cells expressing cRBP-1 antigen (Fig. 3C), also seen in some hepatoid tumour cells (Fig. 3C). Tumour cells showed membranous expression of beta catenin antigen (not shown). There were findings suggestive of delamination of stellate cells from the mesothelium, in the sections stained with desmin antigen (Fig. 3B) and activated hepatic stellate cells expressing alpha SMA in the tumour (Fig. 3D). There was no evidence of tubal carcinoma *in situ* in the fallopian tubes, but there were occasional small cysts with random atypical cells (not shown) and patchy expression of P53 antigen (not shown), also expressed in some adjacent, otherwise morphologically normal, mesothelial cells (not shown).

3. Discussion

Hepatoid carcinoma is a rare type of adenocarcinoma arising in extrahepatic sites, expressing alpha fetoprotein and showing morphological resemblance to hepatocellular carcinoma [1]. Hepatoid carcinoma can arise from endodermal and urogenital organs, the stomach being one of the more common sites (estimated at 84%), other reported sites including lungs, duodenum, jejunum, colon, kidney, pancreas, gallbladder, urinary bladder, peritoneum, testis and ovary [2,3]. In the ovary, there may be a component showing a more common form of