10.1515/chilat-2015-0011

CASE REPORT

Malignant Neighbours in Liver: Co-Occurrence of Metastatic Colorectal and Hepatocellular Carcinomas

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Summary
As the cancer incidence is high and oncologic treatment has improved worldwide, a second primary tumour can threaten the patient. Such situation demands correct management, and can also provide an insight in the mechanisms of carcinogenesis. Here we report a surgically treated 54-year-old female with recurrent colorectal cancer showing close colocalisation of hepatocellular carcinoma arising in non-cirrhotic liver and metastatic colorectal adenocarcinoma. To the best of our knowledge, only few such cases have been reported, mostly from areas characterised by high incidence of hepatocellular carcinoma.
Key words: colorectal cancer, hepatocellular carcinoma, multiple primary cancers

AIM OF DEMONSTRATION

The aim of our report is to show a rare case of a hepatocellular carcinoma in non-cirrhotic liver adjacent to metastatic colorectal adenocarcinoma in order to discuss the clinical occurrence and pathogenesis of multiple primary cancers.

CASE REPORT

A 54-year-old woman with a history of colorectal cancer (CRC) was admitted to a university hospital due to two-day-long obstipation and right abdominal pain. Sixteen months before the present episode, the patient underwent sigmoid resection followed by adjuvant chemotherapy. Fourteen months later, the abdominal ultrasound (US) findings during regular check-up were suggestive of tumour recurrence and multiple focal liver lesions. US-guided liver biopsy yielded the diagnosis of metastatic colorectal adenocarcinoma. On admission, patient's temperature was 36.7°C, heart rate was 72/min. and arterial blood pressure was 130/70 mm Hg. On physical examination, the abdomen was bloated and tender at the right side. No jaundice was apparent. To evaluate the amenability of surgical treatment, computed tomography (CT) was performed and showed hypodense lobulated subcapsular liver lesion in the segments VI and VII without any signs of other segment involvement or biliary stasis (Fig.1). Chest CT did not reveal any suspicious lesions. Considering the well-preserved liver function (Child-Pugh score A5), focal and superficial one-sided liver lesion and no evidence of extensive CRC spread, indications of possible radical operation were set. The patient underwent simultaneous open left hemicolectomy and resection of liver segments VI and VII. Intraoperative US was applied to evaluate liver status. The bowel continuity was restored with primary anastomosis. The operation lasted 440 min. Altogether, 800 mL of packed red blood cells and 500 mL of fresh frozen plasma were transfused during the operation. Histologic examination of the liver specimen (Fig.2) revealed metastatic moderately differentiated colorectal adenocarcinoma, measuring 7 cm, and an adjacent small (0.3 cm) highly differentiated (pT1N0G1R0) hepatocellular carcinoma (HCC). Regarding HCC risk factors, there were no inflammatory or fibrotic changes of the remote liver (hepatitis activity index by Knodell, 0), no steatosis or hemochromatosis. The patient had no previous history of viral hepatitis. In the removed large bowel, an invasive moderately differentiated adenocarcinoma was present (rpT4aG2N0M1aR0). No postoperative complications occurred and the patient was discharged on the 8th postoperative day. Repeated chemotherapy was also recommended.

DISCUSSION

The high incidence of malignant tumours along with remarkably improved treatment worldwide establishes background for the development of multiple primary cancers defined according to the criteria of Warren and Gates as the presence of two or more independent primary neoplasms (6,12). The frequency of such finding ranges 0.3 – 16.0% (6,14). Compared to other neoplasms, colorectal cancer especially frequently is preceded, followed or diagnosed together with other primary malignant tumour: 8.3 – 10% of CRC cases (6,14). The risk of developing subsequent non-colorectal cancer among CRC survivors is significantly increased as revealed by SIR = 1.24; 95% CI = 1.18 – 1.31 (2). HCC, in contrast to CRC, is followed by other primary cancer only in 1% of cases. Statistically significant risk deficit for HCC in females diagnosed with CRC has been reported as characterised by SIR = 0.76, $p < 0.05$ (6).

Our case represents a rare combination of primary HCC and CRC. Only few studies analysing the malignancies associated with CRC have identified patients with both colorectal and liver primary tumours (4,13). These data are mostly from regions of high incidence of HCC and lack detailed analysis of cases (3). Few case reports concerning multiple primary cancer patients with CRC and HCC are available (1,10,12).

The relative risk of multiple primary cancers is higher in younger (aged 20 – 59 years) survivors of CRC (2). Presence of multiple primary tumours and young

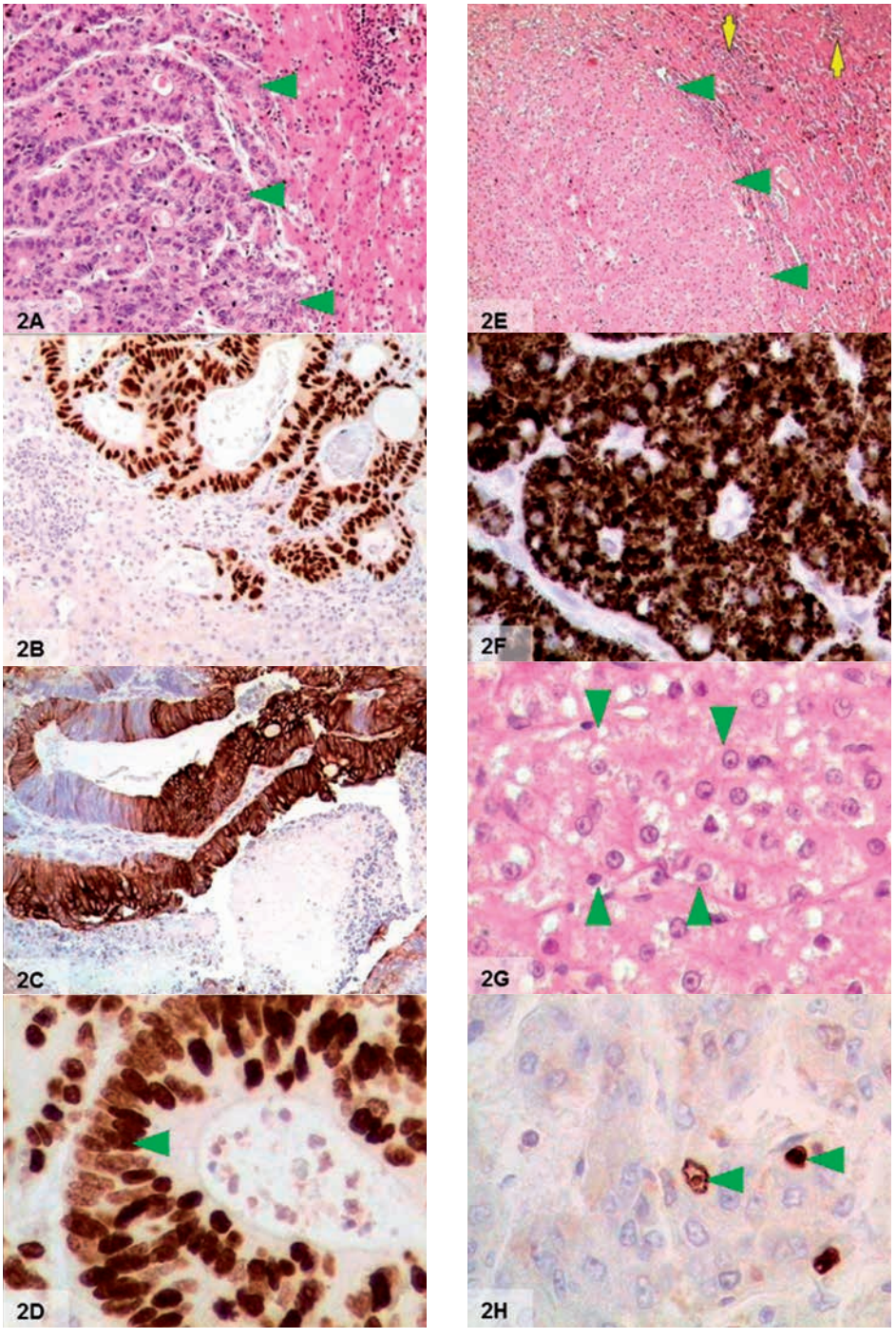

Fig. 2. Histologic findings in the resected liver. 2A – 2D, Liver metastasis of colorectal adenocarcinoma. 2A, General overview. The invasive border is highlighted by green arrowheads. Note the glandular differentiation. Haematoxylin-eosin (HE), original magnification (OM) 100x. 2B, Intense nuclear expression of CDX2. Immunoperoxidase (IP), OM 100x. 2C, Intense heterogeneous cytoplasmic expression of cytokeratin 20. IP, OM 100x. 2D, High proliferation fraction by Ki-67 (clone MIB-1). A representative proliferating cell is highlighted by the arrowhead. IP, OM 400x. 2E – 2H, Hepatocellular carcinoma. 2E, Hepatocellular carcinoma. The invasive border is highlighted by green arrowheads. Note presence of portal fields (yellow arrows) in liver parenchyma adjacent to the nodule and lack of such structures in the carcinoma tissues. HE, OM 50x. 2F, Cytoplasmic expression of TTF-1. IP, OM 100x. 2G, Thickened trabeculae in hepatocellular carcinoma. HE, OM 400x. 2H, Low proliferation fraction by Ki-67 contrasting with colorectal adenocarcinoma. Two of the few proliferating cells are highlighted by arrowheads. IP, OM 400x.

age of onset are characteristics of inherited CRC syndromes (7). Thus, some authors have attributed most of subsequent primary cancer burden to the Lynch syndrome (4). In addition, patients developing multiple primary cancers also are significantly more frequently affected by proximal CRC exhibiting microsatellite instability (8). However, there is no known hereditary cancer syndrome characterised by strong association between HCC and CRC (7). Nevertheless, some genetic background may exist (9). Other possible explanations for increased both HCC and CRC risk are shared lifestyle or environmental exposures, treatment for the initial cancer, or a combination of these effects (1,2). The association between hepatitis C infection and colorectal adenomas has recently been shown (11). Though, there was no evidence of chronic hepatitis C in our patient, and the liver histology outside the mass lesions was bland. Considering the close colocalisation of HCC and metastatic CRC in non-cirrhotic liver, biologically active substances, e.g., tumour necrosis factor alpha, transforming growth factor, insulin like growth factor, epidermal growth factor or endogenous oxidative stress can be involved (3,5).

Study from Taiwan demonstrated 8 patients with HCC and CRC. Most of these HCC cases (6/8) occurred after CRC. This association was significant (13). This fact and our case emphasize the role of surveillance after CRC resection, not only in controlling possible local recurrence and metastatic spread, but also in detection of new primary tumours.

In conclusion, patients affected by colorectal cancer can develop not only metastases but also second primary cancer, including hepatocellular carcinoma. Surveillance must be arranged to establish the diagnosis of subsequent primary tumours properly.

Conflict of interest: None

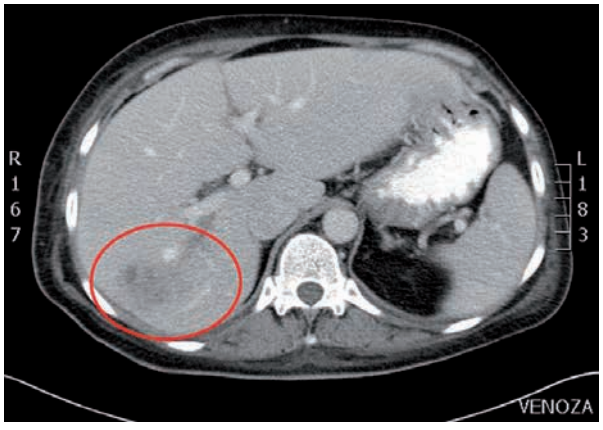

Fig. 1. Contrast-enhanced abdominal computed tomography findings in the venous phase. Note the hypodense liver mass (encircled).

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