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CASE REPORT

A rare case of hepatocellular carcinoma metastasizing hematogenously to the rectum

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Abstract Metastasis to the gastrointestinal tract from hepatocellular carcinoma is uncommon. Herein, we report a rare case of with a metastatic lesion in the rectum, which resembled a primary rectal cancer. An 82-year-old Japanese woman, who had been diagnosed with liver cirrhosis and hepatocellular carcinoma due to chronic hepatitis C, was admitted for further examination of bloody stool. She had undergone radiofrequency ablation twice and transarterial chemoembolization twice before the admission. A colonoscopy revealed a protruding rectal tumor, which was confirmed by biopsy to be poorly differentiated adenocarcinoma. Meanwhile multiple liver recurrences were recognized by an abdominal computed tomography scan. To improve her symptoms and resume the treatment of hepatocellular carcinoma, laparoscopic anterior resection of the rectum was performed to remove the primary rectal cancer. To our surprise, detailed histological examination confirmed that the rectal tumor was a metastatic lesion from the hepatocellular carcinoma.

Keywords Hepatocellular carcinoma · Metastasis · Rectum · Hematogenous spread

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Introduction

Hepatocellular carcinoma (HCC) is one of the leading causes of cancer-related death in the world [1]. Extrahepatic metastases of HCC are not rare, spreading mostly to the lung, the intraabdominal lymph nodes, the bone, and/or the adrenal gland [2–6]. In contrast, gastrointestinal (GI) tract metastasis is uncommon, being found only in 3–12 % of cases at autopsy [5–7]. The most common sites of involvement were the duodenum [8–12], the stomach [9, 10, 13–16], the jejunum [14, 16–18], and the right-sided colon [19–21]. In the literature, there were only a few reports describing the rectal metastasis from HCC. Here, we report a rare case of metastatic HCC in the upper rectum.

Case report

An 82-year-old Japanese woman had been diagnosed with liver cirrhosis and HCC one and a half years before consulting with us. She had first undergone radiofrequency ablation to the solitary HCC at the anterior segment of the liver. The HCC relapsed repeatedly, and she had undergone radiofrequency ablation once more and transcatheter arterial chemoembolization twice for the treatment of each recurrence. Follow-up computed tomography (CT) scans, taken at three months after the last treatment, revealed no evidence of HCC recurrence, while the serum level of alpha fetoprotein (AFP) was gradually increased up to 685 ng/ml. After a month, she was referred to our institute for further examination of an increased AFP level and her additional complaint of bloody stools. Colonoscopy revealed a pale-colored, 20 mm in size, semicircumferential protruding tumor at the upper rectum, which looked

like a common type 2 rectal cancer. Barium enema study showed a filling defect at the upper rectum (Fig. 1). On contrast enhanced CT scans, the rectal tumor was detected as a slightly enhanced, poorly demarcated mass, 20 mm in size, on the right posterior wall of the rectum (Fig. 2a). Histological examination of the biopsied specimen showed that the predominant feature was a poorly differentiated adenocarcinoma rather than a moderately differentiated adenocarcinoma. We diagnosed the rectal tumor as a primary rectal carcinoma by its macro- and microscopic morphology, and failed to check other possible diagnoses at that time by immunohistochemical staining of the biopsied specimen from the rectal tumor. Whole abdomen CT scans also detected three new liver nodules, 35 mm in size at the lateral segment, 25 mm in size at the posterior segment, and 10 mm in size at the left medial segment (Fig. 2b–d). All of these liver nodules are clearly enhanced in the arterial phase and were faded out in the portal venous phase. All were suspected to be recurrent HCC because of the specific enhancement patterns, and there was no evidence of metastatic lesions from the rectal carcinoma. Serological data on the day of colonoscopic examination were as follows: glutamic transpeptidase, 30 IU/l; glutamic oxaloacetic transaminase, 15 IU/l; albumin, 3.4 g/dl; total bilirubin, 0.7 mg/dl; AFP, 3024 ng/ml; white blood cell count, 2400/μl; hemoglobin, 9.0 g/dl; platelet, 5.8×10^4/μl; and positive for hepatitis virus C antibody. Upper endoscopic examination showed no evidence of esophageal nor gastric varices.

Inspite of the presence of multiple HCC recurrences, we decided to resect the rectal tumor, which, if left intact, would interrupt the subsequent treatment for the HCC recurrences due to continual bleeding. Since her performance status was satisfactory and it was thought that she could tolerate surgery, Hartmann's operation was performed laparoscopically to minimize the risk of surgical complications. The postoperative course was uneventful except for the retention of ascites, which was controllable by the use of diuretic agents. The patient was discharged on the 19th postoperative day.

Histopathological examination of the surgical specimen showed that large tumor nodules were scattered in the submucosal area of the rectum and that medium-sized atypical cells with small nuclei were proliferated in a solid and a thick trabecular growth pattern (Fig. 3). The tumor cells markedly invaded the veins inspite of the lack of high-grade cellular atypia, which was not a typical proliferative pattern seen in primary rectal carcinoma. In addition, the histological features of these cells resembled those of HCC. Further IHC examinations showed that the tumor cells were immunonegative for epithelial markers including cytokeratin CK 7, CK 20, carcinoembryotic antigen and caudal-type homeobox-2, but immunopositive for AFP and glypican-3. There was no evidence of metastasis in the regional lymph nodes. No cancer cells were observed in the serosal layer of the rectum, indicating that HCC cells implanted in the rectum via the blood stream, and not through peritoneal dissemination. From these findings, we made a final diagnosis that the rectal tumor was a metastatic lesion from HCC, and not a primary rectal carcinoma. We chose not to provide any treatment including systemic chemotherapy for HCC recurrence, since the disease was found to be in a far advanced stage and even the local treatment for the liver lesions could cause adverse effects due to the patient's age. The patient died due to esophageal varix rupture at 5 months after the operation.

Discussion

HCC is a highly malignant cancer and the prognosis is not satisfactory at this time due to intra- and extrahepatic metastases [1]. Extrahepatic metastases were detected in 25–65 % of autopsied HCC cases [2–6]. The most frequent sites of extrahepatic metastasis were the lung, abdominal

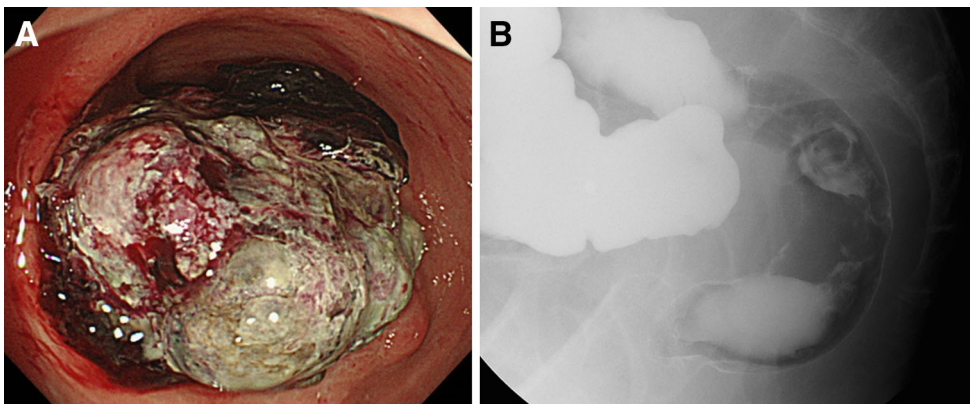

Fig. 1 Preoperative evaluation of the rectal tumor. **a** A colonoscopy showed a semicircumferential, protruding tumor of 20 mm in size at the upper rectum. The tumor was prone to bleeding on contact. **b** Barium enema examination showed a filling defect at the upper rectum

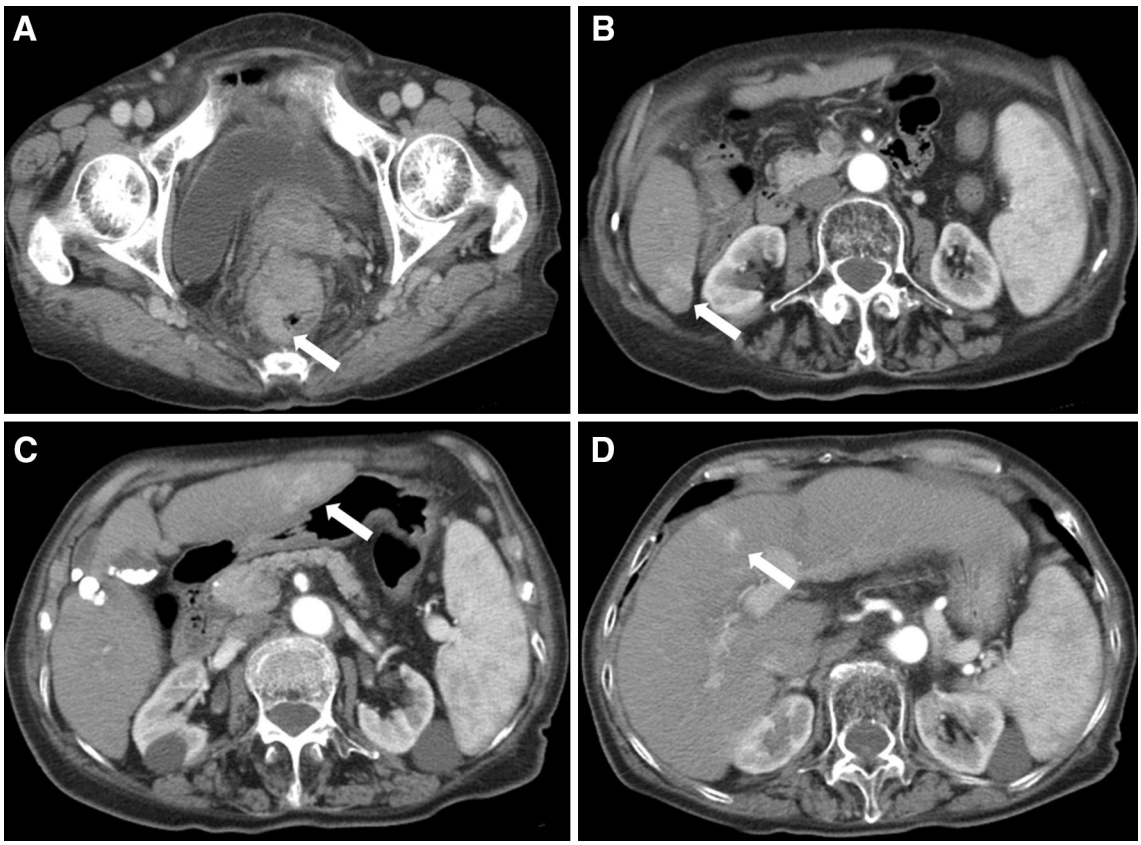

Fig. 2 Preoperative contrast-enhanced computed tomography of the whole abdomen. **a** A slightly enhanced mass was detected at the upper rectum. **b–d** There were three nodules evident in the liver, which were suspected to be recurrent HCC lesions (35 mm in S3, 25 mm in S6, and 10 mm in S4)

lymph nodes, bone, and adrenal grand. However, metastatic lesions in the GI tract were revealed only in 3–12 % of autopsied HCC cases [5–7]. Among the few reports describing hematogenous metastasis to the GI tract, the most common metastatic sites are the upper GI tract, the small bowel, or the ascending colon, while metastasis to the left-sided colon or the rectum is extremely rare [8–21]. To date, eight cases of hematogenous metastasis from HCC to the colon or the rectum were reported in the English literature (Table 1). Since these metastatic lesions are usually asymptomatic, most were detected on postmortem examination. In the literature, only 0.5–2 % of the cases of GI tract metastasis were detected during the treatment period [9, 14]. Metastatic GI tract lesions from HCC showed a variety of endoscopic appearances including ulcerative, polypoid, or submucosal tumors, sometimes mimicking primary GI carcinomas. In this case, the rectal tumor was confirmed to be a HCC recurrence by IHC staining of the resected specimens. Thus, IHC examination can be useful for making a precise diagnosis of GI tumors with uncommon features in patients with advanced HCC. Before the operation, we prejudged that the tumor was a primary rectal cancer, since a metastatic rectal tumor from HCC is very rare and the rectal tumor appeared as a typical primary cancer on colonoscopy. We should have checked other possible diagnoses preoperatively by immunohistochemical staining of the biopsied specimen from the rectal tumor. We reviewed and immunostained the biopsied specimen after the final pathological diagnosis was established. The tumor cells of the specimen were homogenously immunopositive for glypican-3 (Fig. 4), and immunonegative for CK 20 and caudal-type homeobox-2 (data not shown). If these results were available before the rectal resection, we could have figured out the pathogenesis of the rectal tumor and have discussed the pros and cons of the operation. As one of the palliative treatment, we might have suggested a rectal resection to alleviate the hemorrhage from the tumor. Regarding useful IHC analysis markers, CK 7 and CK 20 are sensitive and specific to tumors of colorectal origin especially when used in combination [22], whereas neither CK 7 nor CK 20 was expressed in 9 out of 11 HCC cases [23]. Caudal-type homeobox-2 was expressed in 97 % of colorectal adenocarcinomas [22], and is used as a highly sensitive and specific marker for differential diagnosis [24]. In contrast, glypican-3 was expressed strongly and specifically in HCC

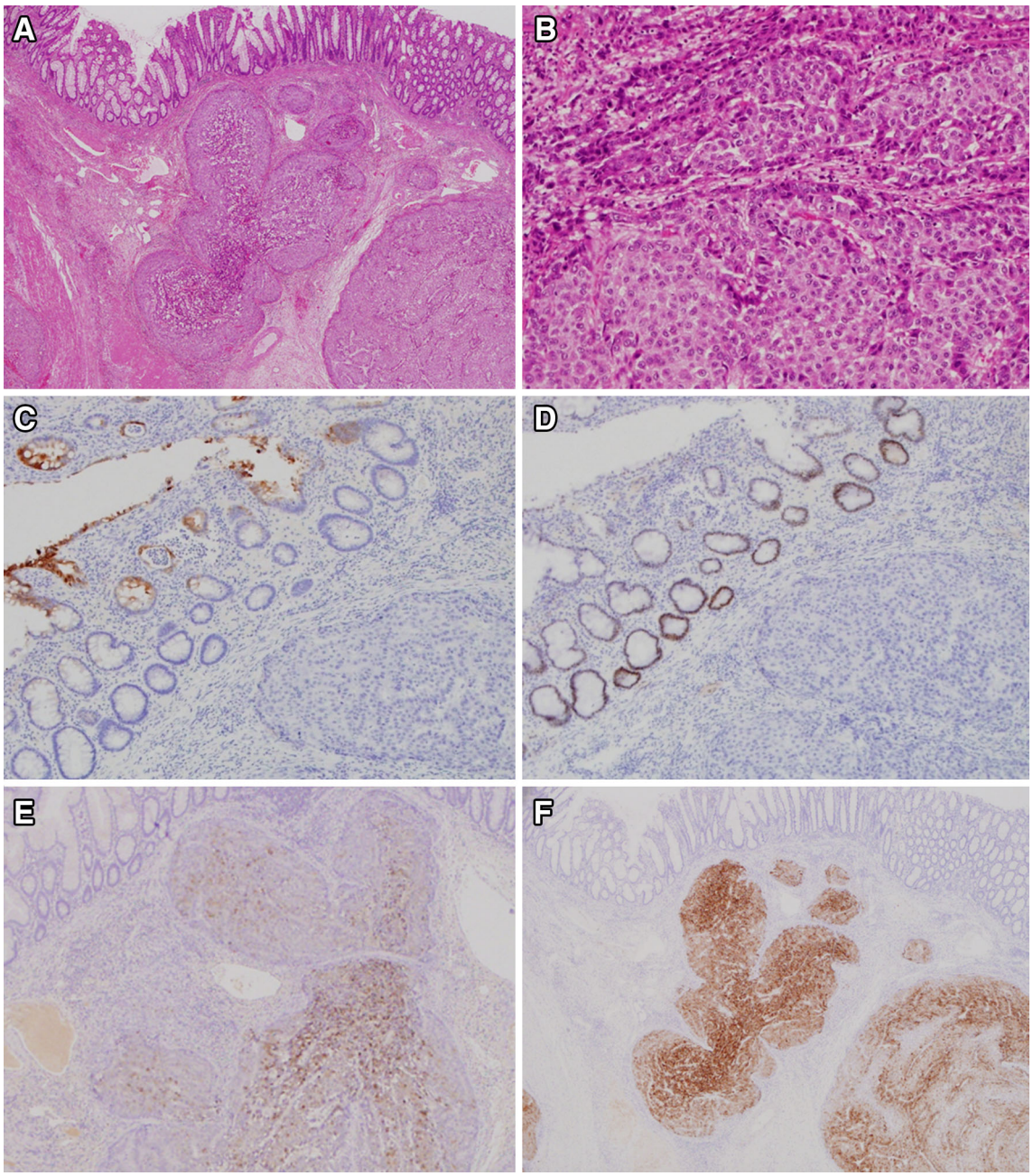

Fig. 3 Pathological and immunohistochemical findings of the rectal tumor. **a** Large tumor nodules were scattered at the submucosal area of the rectum. **b** Medium-sized atypical cells with small nuclei were proliferated in a solid and a thick trabecular growth pattern. These pathological findings were uncommon in rectal carcinomas. Immunohistochemical staining showed that the tumor cells were immunonegative for cytokeratin 20 (**c**) and caudal-type homeobox-2 (**d**) but immunopositive for alpha-fetoprotein (**e**) and glypican-3 (**f**)

cells, and is a reliable marker for the diagnosis of HCC [25]. Another specific marker for HCC is AFP, which was expressed in 70–90 % of HCC cases [26].

It is intriguing that there was no evidence of serosal invasion of the rectal tumor while severe venous invasion was observed by histopathological examination. Through hepatofugal flow in the portal venous system, tumor cells can theoretically travel from the liver to the GI tract via the blood stream. It is well known that the liver, complicated with hepatocellular carcinoma, shows specific changes in the hemodynamics of its blood flow, including portal hypertension and consequent reduction of portal blood flow followed by a compensatory increase of hepatic arterial blood flow. By analyzing angiographic findings in 49 liver cirrhosis and 47 primary HCC cases, Okuda et al. concluded that retrograde portal flow is rarely associated with

Table 1 Profiles of the patients with haematogenous metastases of hepatocellular carcinoma to the colon or the rectum

Case	Report (year)	Age	Sex	Metastatic sites[a]	Symptoms	Interval[b]	Treatment for metastasis	Survival[c]	PVT	Aetiology
1	Fukui et al. (1993)	57	M	A	Fecal occult blood	56	NA	NA	Absent	HCV
2	Cosenza et al. (1999)	82	F	A	Fecal occult blood	73	Surgery	>25	Absent	HCV
3	Tapuria et al. (2007)	67	M	A	Maelena	Simultaneous	Bypass surgery	A few months	Present	Autoimmune
4	Ng et al. (2007)	35	M	A	Bloody stool	6	Surgery	>60	Absent	HBV
5	Yoo et al. (2010)	47	M	S	Abdominal pain	18	Surgery	NA	Absent	HBV
6	Ou et al. (2014)	62	M	A and R	Bloody stool, tenesmus	38	Polypectomy	1	Absent	HBV
7	Nielsen et al. (2014)	51	M	RS	Abdominal pain, diarrhea	30	Chemotherapy	NA	NA	HBV
8	Our report	83	F	R	Bloody stool	17	Surgery	5	Absent	HCV

HBV hepatitis B virus; *HCV* hepatitis C virus; *PVTT* portal vein tumor thrombosis;

[a] Metastatic sites; *A* ascending colon; *S* sigmoid colon; *R* rectum; *RS* rectosigmoid

[b] Time interval between the diagnosis of hepatocellular carcinoma and colorectal metastasis (months)

[c] Survival time after the diagnosis of colorectal metastasis (months)

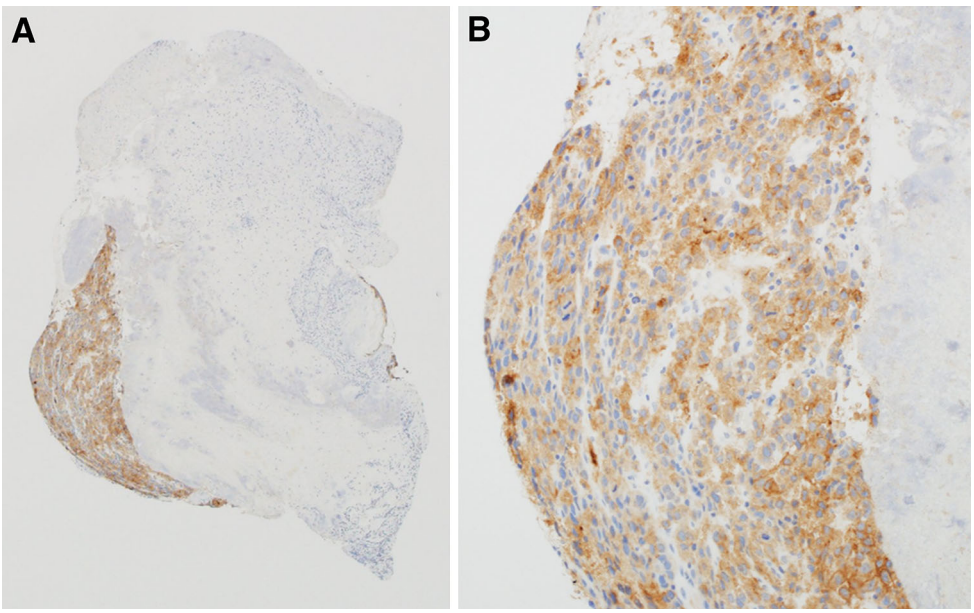

Fig. 4 Immunohistochemical findings of the biopsied specimen from the rectal tumor. The tumor cells were homogenously strongly immunopositive for glypican-3

liver cirrhosis and is more frequently evident in the liver with primary HCC [27]. Furthermore, according to their analyses, in many cases with severe liver cirrhosis, cancer cells easily flowed directly into the greater circulation via collateral blood flow without remaining confined to the mesenteric veins. Therefore, some primary HCCs may

have the potential to metastasize to the GI tract hematogenously due to portal vein backflow, especially when the malignancy develops in the liver with slight or mild cirrhosis before the collateral blood circulation is fully formed. Thus, we speculate that the route of the metastasis in this case was via the blood stream, rather than via peritoneal dissemination.

With regard to the prognosis of patients with metastatic HCC in the GI tract, the median survival from the detection of the GI tract metastasis was 2.1 months, ranging from 2 weeks to 17 months [8, 9, 12–14]. In this case, the patient survived for more than 4 months after the diagnosis of metastasis of HCC to the rectum, but eventually died due to esophageal varix rupture.

In conclusion, we reported a very rare case of HCC metastasizing to the upper rectum, where the metastatic rectum tumor appeared as a common type 2 rectal carcinoma, and not a submucosal tumor. We also provided a review of the literature related to this case.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Parkin DM, Bray F, Ferlay J, Pisani P (2005) Global cancer statistics, 2002. CA Cancer J Clin 55:74–108
2. Edmondoson HA, Steiner PE (1954) Primary carcinoma of the liver: a study of 100 cases among 48,900 necropsies. Cancer 7:462–503
3. Kay CJ (1964) Primary hepatic cancer. Review of ninety-six cases. Arch Intern Med 113:46–53
4. Sung JL, Wang TH, Yu JY (1967) Clinical study on primary carcinoma of the liver in Taiwan. Am J Dig Dis 12:1036–1049
5. Anthony PP (1973) Primary carcinoma of the liver: a study of 282 cases in Ugandan Africans. J Pathol 110:37–48
6. Nakashima T, Okuda K, Kojiro M et al (1983) Pathology of hepatocellular carcinoma in Japan. 232 consecutive cases autopsied in ten years. Cancer 51:863–877
7. Katyal S, Oliver JH, Peterson MS et al (2000) Extrahepatic metastases of hepatocellular carcinoma. Radiology 216:698–703
8. Arima K, Suga M, Ikeda N et al (1992) Hepatocellular carcinoma with metastasis to the duodenum: a case report. Dig Endosc 4:62–67
9. Lin CP, Cheng JS, Lai KH et al (2000) Gastrointestinal metastasis in hepatocellular carcinoma: radiological and endoscopic studies of 11 cases. J Gastroenterol Hepatol 15:536–541
10. Park MS, Kim KW, Yu JS et al (2014) Radiologic findings of gastrointestinal tract involvement in hepatocellular carcinoma. J Comput Assist Tomogr 26:95–101
11. Hung GU, Yeh YH, Chen YL et al (2008) Duodenal metastasis from hepatocelluar carcinoma demonstrated on FDG PET/CT imaging. Clin Nucl Med 33:859–860
12. Chung C, Al Ali J, Owen DA et al (2009) A rare case of isolated duodenal metastases from hepatocellular carcinoma associated with p53 and ki-67 expression: a case report. Cases J 2:9344
13. Makino H, Takazakura E, Nakamura S et al (1986) Hepatocellular carcinoma with metastatic gastric cancer simulating Borrmann type 2 and hyperlipidemia. Acta Pathol Jpn 36:577–586
14. Chen LT, Chen CY, Jan CM et al (1990) Gastrointestinal tract involvement in hepatocellular carcinoma: clinical, radiological and endoscopic studies. Endoscopy 22:118–123
15. Yoshikawa I, Murata I, Tabaru A et al (1994) Metastatic hepatocellular carcinoma of the stomach presenting as a bleeding polypoid lesion. Dig Endosc 6:248–252
16. Yang PM, Sheu JC, Yang TH et al (1987) Metastasis of hepatocellular carcinoma to the proximal jejunum manifested by occult gastrointestinal bleeding. Am J Gastroenterol 82:165–167
17. Kim HS, Shin JW, Kim GY et al (2006) Metastasis of hepatocellular carcinoma to the small bowel manifested by intussusception. World J Gastroenterol 12:1969–1971
18. Iwaki K, Ohta M, Ishio T et al (2008) Metastasis of hepatocellular carcinoma to spleen and small intestine. J Hepatobiliary Pancreat Surg 15:213–219
19. Fukui H, Kashiwagi T, Shirai Y et al (1993) Metastasis of hepatocellular carcinoma to the colon demonstrated by Tc-99 m PMT scintigraphy. Clin Nucl Med 18:512–515
20. Cosenza CA, Sher LS, Poletti BJ et al (1999) Metastasis of hepatocellular carcinoma to the right colon manifested by gastrointestinal bleeding. Am Surg 65:218–221
21. Tapuria N, Sinha CK, Michael NG et al (2007) Haematogenous metastasis to ascending colon in a patient with hepatocellular carcinoma and autoimmune hepatitis. Eur J Gastroenterol Hepatol 19:607–609
22. Bayrak R, Haltas H, Yenidunya S (2012) The value of CDX2 and cytokeratins 7 and 20 expression in differentiating colorectal adenocarcinomas from extraintestinal gastrointestinal adenocarcinomas: cytokeratin 7-/20+ phenotype is more specific than CDX2 antibody. Diagn Pathol 7:9
23. Chu P, Wu E, Weiss LM (2000) Cytokeratin 7 and cytokeratin 20 expression in epithelial neoplasms: a survey of 435 cases. Mod Pathol 13:962–972
24. Werling RW, Yaziji H, Bacchi CE et al (2003) CDX2, a highly sensitive and specific marker of adenocarcinomas of intestinal origin: an immunohistochemical survey of 476 primary and metastatic carcinomas. Am J Surg Pathol 27:303–310
25. Capurro M, Wanless IR, Sherman M et al (2003) Glypican-3: a novel serum and histochemical marker for hepatocellular carcinoma. Gastroenterology 125:89–97
26. Kojiro M, Kawano Y, Isomura T et al (1981) Distribution of albumin- and/or alpha-fetoprotein-positive cells in hepatocellular carcinoma. Lab Invest 44:221–226
27. Okuda K, Moriyama M, Yasumoto M et al (1973) Roentgenologic demonstration of spontaneous reversal of portal blood flow in cirrhosis and primary carcinoma of the liver. Am J Roentgenol 119:419–428