

โรคมะเร็ง 2 ชนิดที่พบพร้อมกัน ระหว่างโรคมะเร็งไส้ตรงกับมะเร็งตับ

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บทคัดย่อ การพบโรคมะเร็ง 2 ชนิดพร้อมกัน ระหว่างโรคมะเร็งไส้ตรงกับมะเร็งอื่น ๆ ทั่วโลกยังมีรายงานน้อยมากจวบจนปัจจุบัน ดังนั้น เราจึงเขียนรายงานนี้เสริมอีกหนึ่งราย ที่เกิดขึ้นพร้อมกัน ระหว่างมะเร็งไส้ตรงกับมะเร็งตับ โดยผู้ป่วยเป็นชายไทย อายุ 65 ปี มาตรวจด้วยอาการถ่ายเป็นเลือดสด 2-3 วัน ไม่มีไข้ น้ำหนักไม่ลด ตรวจร่างกายไม่พบสิ่งผิดปกติ ส่งกล้องตรวจทางทวารหนักพบก้อนเนื้ออกที่ไส้ตรงกับติ่งเนื้อในลำไส้ใหญ่หลายตำแหน่ง ตรวจช่องท้องทั้งหมดด้วยเอกซเรย์คอมพิวเตอร์ ก็ยืนยันถึงเนื้ออกที่ไส้ตรงและยังพบก้อนเนื้อที่ตับและตับแข็ง ตรวจเลือดพบ Hematocrit (HCT) 37.7% Carcinoembryonic antigen (CEA) 22.04 นาโนกรัม/มิลลิลิตร ระดับ alpha-fetoprotein (AFP) ปกติ พบไวรัสตับอักเสบ บี albumin 3.1 กรัม% และ globulin 3.6 กรัม% ผู้ป่วยได้รับการผ่าตัดก้อนเนื้อที่ไส้ตรง ตีงในลำไส้ใหญ่ และตัดก้อนเนื้อที่ตับ พร้อมต่อปลายลำไส้ใหญ่ออกทางหน้าท้องและรักษาต่อด้วยการฉายแสงและยาเคมีบำบัด ซึ่งประกอบด้วย 5-fluorouracil และ leucovorin ผลพยาธิวิทยาเนื้ออกของไส้ตรงพบว่า เป็นมะเร็ง Adenocarcinoma ส่วนของตับพบว่า เป็นมะเร็งชนิด Hepatocellular carcinoma จากนั้น 9 เดือนหลังการรักษาพบว่า ระดับ CEA ในเลือดปกติ เอกซเรย์คอมพิวเตอร์ในช่องท้องไม่พบเนื้ออกกลับมาอีกทั้งบริเวณตับและผนังลำไส้ โดยผู้ป่วยยังคงมีชีวิตรอดถึง 3 ปี ขณะที่เขียนรายงานนี้ แม้ว่ามะเร็งปฐมภูมิของลำไส้ใหญ่และไส้ตรงที่กระจายไปที่ตับจะพบบ่อยกว่ามะเร็งปฐมภูมิ 2 ชนิดที่พบพร้อมกัน ระหว่างโรคมะเร็งไส้ตรงกับมะเร็งตับมากแค่ไหน เราต้องไม่ละเลยการตัดสินใจเนื้ออกของตับ ต่อให้ระดับ AFP ในเลือดจะไม่เพิ่มขึ้นก็ตาม มิฉะนั้นแล้ว โรคมะเร็ง 2 ชนิดที่พบพร้อมกันก็จะถูกมองข้ามไปได้ นอกจากนี้ โรคมะเร็งตับก็จะไม่ได้รับการจัดการอย่างเหมาะสม ในเรื่องของความสัมพันธ์ระหว่างโรคมะเร็งไส้ตรงกับมะเร็งตับจะได้รับการวิจารณ์ในรายละเอียดต่อไป (วารสารโรคมะเร็ง 2567;44:184-193)

คำสำคัญ: โรคมะเร็ง 2 ชนิดที่พบพร้อม โรคมะเร็งไส้ตรง โรคมะเร็งตับ

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Synchronous Double Primary Cancers of Adenocarcinoma of The Rectum and Hepatocellular Carcinoma

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Abstract Synchronous double primary cancers of the rectum and another have been hardly reported worldwide, so far. So, we additionally presented one patient who concurrently developed synchronous double cancers of the rectum and the hepatocellular carcinoma. He was a 65-year-old Thai who presented with hematochezia for a few days without fever or weight loss. His physical examination did not reveal any significant abnormality. The colonoscopy found a rectal mass and multiple colonic polyps. The computerized tomography of the whole abdomen confirmed the rectal mass and also another mass in the liver with cirrhosis. His blood tests showed HCT 37.7%, elevated carcinoembryonic antigen (CEA), 22.04 ng/ml and normal alpha-fetoprotein (AFP) level, positive hepatitis B virus antigen, albumin 3.1 g% and globulin 3.6 g%. He underwent low anterior resection of the rectal mass, multiple colonic polypectomy, segmentectomy of the liver mass and colostomy and was further treated with radiation and adjuvant chemotherapy consisting of 5-fluorouracil and leucovorin. The pathology of the rectal mass was adenocarcinoma whereas the liver mass was hepatocellular carcinoma. Nine months after treatment, the serum level of CEA appeared normal and the CT of the abdomen showed no recurrence of the liver or bowel wall carcinoma. He could still survive up to three years when this report was written. Although the primary colorectal cancer with liver metastasis is much more common than the synchronous double primary cancers of the colorectum and the liver, the liver mass biopsy must not be ignored even though the serum AFP level is not elevated, otherwise the double cancers can be overlooked and the appropriate management of the liver carcinoma will have never been accessed. The association between both cancers will be further discussed in detail. (*Thai Cancer J* 2024;44:184-193)

Keywords: double cancers, rectal carcinoma, liver carcinoma

Introduction

The simultaneous occurrence of two pathologically different cancers in the same individual, the so-called synchronous double cancers, have been rarely reported whereas the primary cancer with its distant metastatic lesion is much more commonly found. Therefore, when two tumor masses which are documented in different organs are found in practice, they are always presumed to be one primary cancer and its secondary distant metastasis. Likewise, because synchronous double primary cancers of the rectum and another cancer have been hardly found including the liver cancer which has been globally found as only sequential case reports¹⁻⁵. On the contrary, the liver metastasis can be commonly found in the colorectal cancer patients, 26.5% within 5 years of diagnosis⁶ and the liver is the most common site of metastasis of the colorectal cancer, 71% of all metastatic lesions⁷. All these facts may discourage the effort to perform biopsy of the liver and the colorectal lesions, therefore the synchronous double primary cancers of colorectum and the liver can be missed if the pathological verification of both sites is not demonstrated. The aim of this report was to present the case of the double primary cancers of the rectum and the liver found in an old Thai man.

Case Report

An old Thai man with 65 years of age presented with occasional bloody stools for two months. He also had peri-anal pain any time when he passed stool but had no fever or weight loss. He did not smoke or drink. There was no family member having colorectum cancer diagnosed. The physical examination revealed no significant abnormality. His initial blood test showed Hb 13.0 g%, Hct 37.7%, WBC 5,940/mm³, N 68%, L 22%, platelet 142,000/mm³, MCV 82.5 fl. and MCH 28.4 pg. He underwent colonoscopy which revealed a rectal mass, 3.1x5.0 cm with blood oozing mucosa and many sessile colonic polyps: one 2-cm at the descending, two 0.5-cm at the transverse and one 1-cm and another 0.5-cm at the hepatic flexure of the colon. The esophagogastroduodenoscopy showed acute mild gastritis, duodenitis, no H. pylori detected, no intestinal metaplasia, and no malignancy. The multi-modality computerized tomography of the whole abdomen confirmed the enhancing rectal mass, 5.1x5.0x7.9 cm in length and 4.6 cm from the anal verge. The liver showed mild nodular surface, probably mild cirrhosis. A 3.5x3.2 cm arterial enhancing liver mass at the segment 5 with washout in portal and delayed 5 min phase. The differential diagnoses were Hepatocellular carcinoma (HCC), liver metastasis or other arterial enhancing liver masses such

as hepatic adenoma. A 0.6-cm hypodense nodule at subcapsular region of the segment 4; too small to characterize. Multiple sub-centimeter lymph nodes at the perirectal, para-aortic, aorto-caval, peri-pancreatic, gastro-hepatic, and gastro-splenic regions were detected.

The histopathology of the rectal mass biopsied via colonoscopy showed tubulovillous adenoma, high-graded dysplasia while the polyps were tubular adenoma, low-graded dysplasia, no malignancy seen. The ultrasound-guided liver mass needle biopsy showed well differentiated HCC.

Other blood tests showed albumin 3.1 g%, globulin 3.6 g%, AST 52 U/L, ALT 38 U/L, alkaline phosphatase 78 U/L (normal 30-120), indirect bilirubin 0.5 mg%, direct bilirubin 0.1 mg%, BUN 9.0 mg%, creatinine 0.99 mg%, eGFR 79.0 ml/min/1.73 m², carcinoembryonic antigen (CEA) 7.74 ng/ml (reference range 0-40), CA 19-9 6.31 U/ml (reference range <37), HBsAg-positive, anti-HBc-positive, anti-HCV-negative, VDRL-negative, TPHA-negative, normal coagulogram, blood sugar 95 mg%, LDL cholesterol 194 mg%, HDL-cholesterol 48 mg%, triglyceride 85 mg%.

The clinical diagnosis was synchronous double carcinoma of the rectum, stage T3N0M0 and the HCC. The operation was the low anterior resection (LAR) to remove the cancer mass including some part of the rectum, multiple colonic polypectomies, colostomy, resection of the surrounding lymph nodes and the liver segmentectomy that harbored the mass. The pathology of the rectal mass was well differentiated adenocarcinoma invading through muscularis propria into peri-rectal tissue, no lymphatic vascular invasion, free proximal, distal and circumferential margins, no carcinoma seen in 22 peri-rectal lymph nodes. The pathology of the liver segment 5 was well differentiated HCC of the solitary tumor, 3.7 cm in greatest diameter, no vascular invasion, free resected margin, and liver cirrhosis was also present.

After operation, he was further treated with the sandwich therapy, viz, adjuvant chemotherapy which consisted of 5-fluorouracil (5-FU) and leucovorin for 6 courses and radiation therapy using the linear accelerator. He could tolerate the treatments well. On the 26th day of the operation, his chest film and CT scan showed massive right pleural effusion that was promptly tapped for study. The pleural fluid showed the adenosine deaminase (ADA) 22 U/L (reference range <40 U/L), lactate dehydrogenase (LDH) 329 U/L with the concurrent serum LDH 172 U/L (reference range 135-225), protein 4,400 mg%, sugar 117 mg%, WBC 320/mm³, RBC 8,500/mm³, N 38%, L 59%, and its cytology showed only inflammatory cells, no malignant cell seen. It was supposed to be reaction after abdominal

operation. Without thoracostomy drainage, the pleural fluid gradually diminished following each cycle of chemotherapy and completely disappeared within four months. Every year after operation, his serial serum CEA continually appeared normal, 2.27, 1.37 and 1.50 ng/ml and his last blood concentration was: Hct 36%, WBC 6,800/mm³, platelet 141,000/mm³, MCV 87.2 fl. and MCH 28.2 pg.

He could survive up to three years after operation when this paper was written, no active hepatitis from hepatitis virus B even though anti-viral agent was offered. The computerized tomography of the whole abdomen each year after operation showed no recurrent mass in the liver or in the residual bowel wall, no pleural effusion and no change of the cirrhosis and the old 0.9-cm liver nodule.

Discussion

The diagnosis of synchronous double cancers of the HCC and the rectal adenocarcinoma in our case was definitely based on the histopathology of the tumor masses resected from the liver and rectum, respectively. If the ultrasound-guided needle biopsy till the HCC could be definitely diagnosed had not been performed, the liver tumor would not have been resected and the liver mass might easily have been presumed to be the liver metastasis from the primary cancer of the rectum. And it is well known that HCC does not well respond to 5-FU⁸, on the contrary, it is considered an essential component for adjuvant chemotherapy for colorectal cancer⁹. Even though either HCC¹⁰ or rectal adenocarcinoma¹¹ is highly prevalent in Thailand, the synchronous double cancers of both the has never been recognized.

The mass in the liver as in our case must be biopsied because he also had cirrhosis incidentally found on the CT with the presence of viral hepatitis B. It is well known that chronic HBV infection with or without cirrhosis is considered the main risk factor for HCC in Thailand¹². Furthermore, even though the serum AFP was within the normal range, hence the liver metastasis from primary rectal carcinoma clinically seemed more likely, the biopsy of the liver mass must not be neglected because up to 47.1% of HCC patients have normal level of AFP. And HCC patients who have AFP within the normal range, they will have fewer early recurrence rate and better disease-free survival¹³.

The computerized tomography of the liver metastasis is typically hypoattenuating on unenhanced and enhancing less than surrounding liver after the contrast¹⁴. On the contrary,

the HCC was shown hyperdense on CT and with contrast, the lesion was hyper-vascular during the earlier phase of enhancement and maximum enhancement during hepatic arterial phase. In the venous phase, the lesion will become hypoattenuating compared with the liver as the result of rapid washout¹⁵. Our case had hepatic lesion which showed arterial enhancing and washout in the venous phase, these encouraged us to search for HCC by performing ultrasound-guided liver biopsy instead of imagination that it was the liver metastasis from the rectal carcinoma.

Our case responded well to multimodality therapy even though he had synchronous double cancers. He could have survived in a good health up to 36 months without recurrence of any malignancy when this report was written. In general, the 5-year survival rate for Barcelona Clinic Liver Cancer (BCLC) stage A, as our case, is 66.3%. Our case did not have 5 poor prognostic factors: AFP > 400, tumor size > 5 cm, multiple tumor nodules, macroscopic vascular invasion, and microscopic portal vein thrombosis therefore, his 5-year survival seems better, 72.9%¹⁶. His normal serum AFP before liver segmentectomy, in combination with the early stage of his HCC without extrahepatic metastasis, he would have better overall survival than those with high AFP¹⁷. Moreover, hepatitis B-related HCC significantly has better survival than those with alcohol or other etiologies¹⁸.

For rectal carcinoma, the median survival for the patients is 101.3 months¹⁹. And its 5-year overall survival rate is 67%²⁰. And because his elevated serum CEA level before treatment became normal and had never been elevated after the radical operation and sandwich therapy, he was expected to have longer survival and better disease-free survival than the patients who have high level of CEA both before and after operation²¹. Nevertheless, three-year interval of our case is too early to evaluate his survival.

The massive pleural effusion in our case was recognized in a few weeks after the abdominal operation. Although it can be found as one complication in any patient who undergoes hepatectomy for hepatocellular carcinoma, 54.5%²² or abdominal surgery for colorectal diseases²³. It also can be malignant pleural effusion spreading from either the liver²⁴ or colorectal carcinoma²⁵. Nevertheless, the cytology of the fluid in our case was shown free from any malignancy whereas the serum CEA was still within the normal range throughout the postoperative period. Furthermore, the mean survival for colorectal cancer who develop malignant pleural effusion is 3.1 ± 1.9 months²⁵. Therefore, the pleural effusion in our case was presumably associated with the abdominal operation for hepatectomy or rectal resection.

And its risk factors included serum albumin < 3.5 g%, the tumor size more than 3 cm and intra-operative blood lost > 500 ml²⁶.

The occurrence of the HCC and the rectal carcinoma in one individual and in the same time may be the co-incidence or imply some possible association. Because both have some common risk factors, e.g., obesity, diabetes, chronic use of alcohol, smoking, diet, including the alteration of gut microbiota²⁷. Our case did not have these risk factors and his gut microbiota had not been studied.

For genetic aspect, some authorities can identify 10 genes which may play an important role as the common pathogenesis for both HCC and colorectal cancer. These comprise CDK1, KIF11, CDC20, CCNA2, TOP2A, CCNB1, NUSAP1, BUB1B, ASPM and MAD2L1²⁸. Nevertheless, all these and other genes study are not explored in our case.

One significant risk factor for isolated HCC is chronic HBV infection and cirrhosis²⁹ whereas one for rectal carcinoma is adenomatous polyposis of the colorectum³⁰. There were one patient with the polyposis coli preceded by the HCC³¹ and another patient with HCC found associated with familial adenomatous polyposis³². On the contrary, besides the HCC, chronic HBV infection is also found to be the significant risk factor of colorectal carcinoma, odd ratio 1.27, 95% confidence interval (CI) 1.20-1.33³³. Moreover, the prevalence of colorectal neoplasia was higher in the HBsAg (+) than in HBsAg (-) participants (16.9% vs. 15.6%, $p = 0.009$)³⁴. And in one prospective study, the adjusted hazard ratio for the association between seropositive HBV and colorectal cancer was 1.85, 95% CI 1.15 - 2.96³⁵. Our case had HBV infection with cirrhosis and multiple adenomatous colonic polyps which might be potentially contributing risk factors for the occurrence of both cancers simultaneously.

Conclusion

A case of synchronous double primary cancers of HCC and rectal adenocarcinoma was found in an old Thai man. He had chronic hepatitis B virus infection with cirrhosis and multiple adenomatous colonic polyps which were supposed to be the contributing risk factors for both cancers therefore the simultaneous occurrence of both cancers in the same individual seems to prefer some association via chronic HBV infection and colonic polyps rather than co-incidence.

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