Case Report
Synchronous triple colorectal carcinoma: a case report and review of literature

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Abstract: Synchronous colorectal carcinoma defines as multiple malignant lesions presented in a single patient at initial diagnosis. We report a case of triple synchronous colorectal carcinoma without related familial history. Preoperative computed tomography (CT) scan and endoscopic examination suggested multiple malignant lesions occurred in separate segments of colon. Then we performed laparoscopic total colectomy and ileorectal anastomosis with a J-type pouch. Post operative pathological examination confirmed the malignant characteristics of the triple lesions. The mini review summarizes the clinicopathological and molecular features of synchronous colorectal carcinoma based on current literatures. It appears to probably have significant distinctions with solitary tumors in terms of pathological type, primary locations and microsatellite instability.

Keywords: Synchronous colorectal carcinoma, case report

Introduction

Synchronous colorectal carcinoma refers to more than one primary cancers discovered in a single patient at initial presentation, which is a special and rarer type of colorectal malignancy compared to solitary tumors [1]. Here we report a case of synchronous triple colorectal carcinoma of a middle-aged male patient and present an associated mini review on current research of synchronous colorectal carcinoma.

Case description

A 51-year-old man sought medical consultation in Gastrointestinal Surgery of Union Hospital presented with a three-month history of hematochezia and intermittent abdominal pain. The patient had no family history of cancer or hereditary intestinal disorders. Physical examination revealed a soft tenderness in the lower left quadrant of the abdomen without any mass palpated. Hemorrhoids or anal fissures were not discovered via digital rectal examination. Regular laboratory examinations demonstrated a hemoglobin level of 83 g/L and the occult blood test was positive as well. Tumor markers were in the normal range (CEA 1.5 μg/L). The abdominal plain film revealed flatulence in splenic flexure and descending colon, while sporadic air fluid levels were presented as well (Figure 1A). Further abdominal contrast CT scan identified a mass lesion in ascending and descending colon with associated circumferential thickening and local infiltration (Figure 1B). The electronic colonoscopy (Figure 1C) and endoscopic ultrasonography (EUS) examination (Figure 1D) were partially blocked in descending colon due to the canal stenosis, showing an iso-echoic polyloid lesion in sigmoid colon (28 cm from anal verge) and suspected malignant lesion in descending colon (ulcerative infiltration type, 50 cm from anal verge). Biopsy confirmed both lesions as adenocarcinoma preoperatively (Figure 1E, 1F).

Based on results of preoperative evaluation, the patient underwent total colectomy in a laparoscopic operation. 10 cm of distal ileum, total colon and partial rectum were removed completely with regional lymph nodes dissection. We constructed a J-type pouch with the residual ileum before ileorectal anastomosis to partially replace the stool storage function of colon.
and rectal ampulla. Postoperative pathological examination confirmed triple synchronous malignant lesions in total colon. Tumor A was a protruding 4.5 cm×4 cm mass in proximal ascending colon (1.5 cm away from ileocecal valve) with moderate differentiation and full thickness infiltration (pT4N0M0). Tumor B was an ulcerative 6 cm×3 cm mass in descending colon (13 cm from distal incisal margin) with moderate differentiation and full thickness infiltration (pT4N0M0). Tumor C was confirmed as a polyoid 1.5 cm×1 cm lesion in sigmoid colon (8 cm from distal incisal margin) with well differentiation and submucosal infiltration (pT1N0M0) (Figure 2). There were no residual tumors and metastasis in incisal margins and regional lymph nodes respectively. Three days later, the patient began liquid diet and the ileal pouch successfully controlled the frequency of defecation to 2-3 times per day after surgery. No severe complications such as anastomotic leakage occurred during hospital stay post-operatively. The TNM clinical grading of this patient was stage II, thus we performed 6 cycles of XELOX regimen as adjuvant therapy and the patient revealed good tolerance and compliance without tumor relapse.

Discussion

Synchronous colorectal carcinoma: epidemiological, clinical, pathological features and molecular mechanisms

Synchronous colorectal carcinoma indicates more than one primary malignant lesions discovered in a single patient simultaneously. Once multiple colorectal cancers are detected in different time points, it is identified as metachronous colorectal carcinoma. The initial presence of multiple tumors is the major point of identification as a synchronous cancer [2].

Synchronous colorectal carcinoma accounts for a wide-range 1%-8% of all colorectal can-
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Cancers by review on different studies [3-5]. Four convincing large sample-size (>800 cases) studies reported a prevalence of 3.1%, 3.7%, 3.9% and 3.5% respectively [3, 6-8]. A systemic review reported an overall incidence of 3.5% of synchronous colorectal carcinoma versus all colorectal cancers by pooling data from 39 studies (3667/105686) [2]. These results suggest synchronous cancers as a relative rare entity with overall incidence rate probably below 4%.

Compared to solitary cancers, synchronous colorectal carcinoma presents a higher male to female ratio indeed [6]. An 884-case study reported a ratio of 1.6 in synchronous colorectal carcinoma in contrast to 1.2 of solitary cancer [3]. By pooling data from the majority of related studies, the male to female ratio was 1.7 in total (2797/1588) [2, 3]. The origination of sex difference is currently unknown, but sex hormones most likely contribute [9]. Therefore further investigations are needed to explain the even more remarkable male predominance in synchronous colorectal carcinoma.

With respect to age, there is no consensus on its correlation with synchronous colorectal carcinoma occurrence. An earlier literature review reported an average age of 63 years when patients presented with synchronous colorectal carcinoma based on large quantity of pooling data [2]. Recent studies presented a discrepant mean-age 47, 72 and 79 years of synchronous cancer patients respectively [3, 10, 11]. Mainstream viewpoint supports a higher presentation age of synchronous cancer patients compared to solitary patients. However, there are still reports of synchronous cancer patients diagnosed at a similar mean-age as solitary patients [6]. Hence, more evidence is needed to elucidate the existence and impact of age disparity.

Location preference of synchronous carcinoma is still in controversy. As is reported that primary locations of synchronous colorectal carcinoma differed from solitary cancers with an ascending colon predominance (43% in synchronous carcinoma to 37% in solitary carcinoma) and less frequency of lesions located in sigmoid colon and rectum compared to that of solitary cancers (48% in synchronous carcinoma to 57% in solitary carcinoma) [3]. Nevertheless, some literature reported a sigmoid advantage of synchronous carcinoma against solitary malignancy [4]. In addition, most synchronous carcinoma is believed to occur separately in different portions of large intestine, with exception of small amount of synchronous carcinoma located closely in the same segment of the colon [8, 12]. These findings are consistent with the right colon predominance of some susceptible factors.

Patients with possible predisposing factors (inflammatory bowel diseases, familial adenomatous polyposis) are reported to have higher risk of synchronous colorectal carcinoma [13-15]. A case series study of inflammatory bowel disease related colorectal cancer presented a surprising ratio of 20% cases diagnosed with synchronous colorectal carcinoma (22/108), which was much higher compared to sporadic incidence rate 3.5% of synchronous carcinoma [14]. Ulcerative colitis is known to overcome Crohn’s disease significantly in triggering synchronous colorectal carcinoma as well [15].

Figure 2. Post operative examination results of this triple synchronous colorectal carcinoma patient. A. Gross morphology of total colon and triple malignant lesions (→); B. A representative image of post operative pathological examination results of tumor A and tumor B (both were moderate differentiated adenocarcinoma); C. A representative image of post operative pathological examination results of tumor C (well differentiated adenocarcinoma); Tissue slides: HE×40.
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study performed by Greenstein and colleagues unveiled that synchronous colorectal carcinoma accounted for 21% of familial adenomatous polyposis related cancer while it merely accounted for 2.5% of de novo colorectal cancer [16]. The reason behind this has been linked to inflammation-induced dysplasia, and adenomas are believed to be more closely involved in development of synchronous tumors especially the serrated sessile adenomas or polyps [4, 17]. In spite of the higher risk of patients with predisposing factors to develop into synchronous colorectal carcinoma, a large-scale study revealed that patients with predisposing factors accounted for only 10% among all synchronous colorectal carcinoma cases [4], suggesting further unknown mechanisms or factors besides predisposing conditions may involve in the development of synchronous colorectal carcinoma.

Whether synchronous colorectal carcinoma possesses specific pathological features has not reached a consensus yet. A retrospective study concluded mucinous adenocarcinoma was slightly more common observed in synchronous colorectal carcinoma than solitary cancers by cases analysis [18]. This result seems rational since mucinous adenocarcinoma is a pathological trait of hereditary nonpolyposis colorectal cancer, which is a common predisposing factor of synchronous cancers. Nevertheless, a convincing series (158 cases) summarized to an opposite result that metachronous cancer but not synchronous carcinoma appeared to have higher ratio of mucinous adenocarcinoma in post-operative pathology examination [19].

More than one primary lesions diagnosed simultaneously is defined as synchronous colorectal carcinoma. Most of the published cases reported only two carcinomas in the large intestine. Patients with three or more primary lesions accounted for 1.8% to 16.7% among all synchronous colorectal carcinoma cases [6, 20]. Up to now, the maximum of tumor count discovered and reported in a single patient is six lesions [21]. Moreover, synchronous colorectal carcinoma is found to display smaller size and lower pathological grading and T staging than standard pathological cancers [15].

The majority of mechanism studies of synchronous colorectal carcinoma blame it on microsatellite instability (MSI) of the genome [22, 23]. Synchronous colorectal carcinoma has a higher proportion of MSI-positive cancers than solitary cancers. There are two responsible mechanisms to generate microsatellite instability in synchronous cancers: 1. With respect to most inherited cases, the hereditary mutation on mismatch repair genes enables the correction process against errors on microsatellite repetition region during DNA replication, resulting in microsatellite instability; 2. In sporadic synchronous cancer patients, methylation of mismatch repair genes mainly results in MSI instead of hereditary factors. Particularly, BRAF related methylation on MLH1 promoters is a strongly indicator for sporadic cases. That is the reason why BRAF is a recommended gene to examine on synchronous colorectal carcinoma patient. The methylation of certain genes may be due to the regional carcinogenic environment of colon and rectum [24-26]. Apart from microsatellite instability, mutations on KRAS and GSRM1 are linked to synchronous cancer as well, revealing a complex mechanism network of carcinogenesis on synchronous colorectal carcinoma [27].

Surgical decision is quite difficult to make since the complex clinical features of synchronous carcinoma and individual differences must be taken into account. Pre-operative examination is necessary for accurate surgical decision. Colonoscopy (including EUS) is an essential approach for the appraisal of tumors count as well as locations and taking a biopsy meanwhile. CT scan is commonly used to make assisted assessment in case of the malignant stenosis and has an advantage on local infiltration evaluation over endoscopy. Even with these measures, there are still some lesions failed to identify preoperatively due to their tiny sizes.

In terms of surgical procedures, a retrospective large scale cohort study represented by van Leersum and colleagues reported that patients with synchronous colorectal carcinoma were more likely to receive deviating or permanent stoma (37% versus 33%) and less likely to undergo a laparoscopic operation compared to solitary cancer patients [3]. The reason may be due to the difficulty in dealing with extensive resection range and more concerns on anastomotic leakage than managing solitary regional cancers. Early-stage lesions can be removed
under colonoscopy. Patients with tumors located in the adjacent segment are recommended for a hemicolectomy, otherwise a sub-total or total colectomy is preferred.

In summary, synchronous colorectal carcinoma is a unique subtype of colorectal cancer and shows great disparity against solitary tumors with all probable clinical and molecular implications confirmed by current studies. However, it is premature to make conclusions with those controversies unsolved and further researches are needed to finally judge.

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Disclosure of conflict of interest

None.

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