Case Report

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Synchronous primary malignancy of colon cancer and mantle cell lymphoma: A case report

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Abstract: Multiple primary malignancies in a single patient are relatively rare; however, the frequency of this has increased significantly in recent decades. Here, we retrospectively reported an unusual case of a 70-year-old man who was admitted to the hospital with mantle cell lymphoma (MCL) and colon cancer and aimed to explore measures to reduce missed diagnosis. Based on the data, the investigation of the related literatures, colonoscopy examination, and abdominal computed tomography (CT) scan were conducted for the detection of colon cancer. Following this, a precise diagnosis of MCL was confirmed by immunohistochemistry and bone marrow biopsy, which were performed to analyze the clinical characteristics and essentials for the diagnosis and differential of the disease. The results of colonoscopy showed that the patient had colon cancer, while the abdominal CT scan demonstrated colon cancer accompanied by multiple lymphadenopathy throughout the entire body. Besides, the results of immunohistochemistry confirmed that the patient suffered from MCL. The bone marrow biopsy revealed the active hematopoietic tissue hyperplasia but no tumor issue involvement in the bone marrow. In conclusion, our study combined the analysis and summary of the

Keywords: multiple primary cancer, colon cancer, mantle cell lymphoma, colonoscopy, computed tomography

1 Introduction

Multiple primary malignancies are defined as the occurrence of two or more malignancies without subordinate relationship in different organs of an individual patient, while the underlying mechanism remains unclear [1]. The incidence of multiple primary malignancy is rare although the prevalence rate is increasing recently [2]. Mantle cell lymphoma (MCL) is a unique B-cell lymphoma that accounts for 3-10% of non-Hodgkin's lymphoma (NHL) with a median survival of 3-4 years [3]. It is more common in the elderly, which is often diagnosed at an advanced stage [4]. Lymph node metastasis in colon cancer and extralateral lymphoma in gastrointestinal tract are common, whereas conventional lymph node biopsy during the operation of colon cancer and partial enlarged lymph nodes that are found in MCL are rare [5]. Only one case reported that a patient developed NHL after curative resection of colon cancer in recent decades, but no report was found about synchronous primary malignancy, including the colon cancer and lymphoma [6]. Herein, we present such an unusual case of colon cancer and MCL. To our knowledge, this is the first article that has been reported on double primary malignancies associated with MCL in a patient with colon cancer. We report the following case according to the CARE reporting checklist.

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2 Case presentation

A 70-year-old man was admitted to our hospital in March 2017 due to upper abdominal pain for more than 2 weeks. He had no obvious nausea, vomiting, chills, fever, black

diagnosis and treatment of the colon cancer with MCL to provide clinical guidance for the rare multiple primary malignancy.

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stools, and other discomforts. The patient was previously healthy and had no family history of colon cancer or malignant lymphoma, and social history was noncontributory.

The colonoscopy revealed colon cancer, and the abdominal computed tomography (CT) indicated colon cancer and systemic multiple lymphadenopathy that might be malignant lymphoma (Figure 1). On March 17, 2017, the pathological diagnoses were as follows: (descending colon) uplifted moderately differentiated adenocarcinoma with a maximum mass diameter of 4.5 cm infiltrating into the serosal layer; the peripheral lymph node metastases were 3/10 perienteric group, 2 cancer nodules, and 0/5 mesenteric group; the upper and lower cutting edges were negative (Figure 2a). The immunohistochemical results showed P53 (3+), Ki-67 (+, about 70%), CEA (+), E-cadherin (+), Topo-II (2+), and CDX-2 (+) (Figure 2b). Fourteen retroperitoneal lymph nodes with a maximum diameter of 0.3-6 cm were found: NHL (Figure 2c). Immunohistochemical results showed LCA (+), CD3 (-), CD20 (+), PAX-5 (+), CD10 (-), Bcl-6 (-), Mum-1 (+), Bcl-2 (+), Ki-67 (+, about 50%), and cyclin D1 (+) (Figure 2d). Finally, the patient was diagnosed as NHL [MCL at stage IIIA, CD20+ with International Prognostic Index (IPI) score of 4 points, postoperative colon cancer (pT3N1M0, stage IIIB)]. During the course of the disease, the patient had no fever, night sweats, or significant weight loss. The bone marrow biopsy on April 10, 2017, revealed that bone marrow hematopoietic tissue hyperplasia was active, and the hematopoietic tissue accounted for about 40% with the degree of hyperplasia (++). Besides, granulocytes proliferate actively, protocells were observed, and the proportion of mature granulocytes was normal.



Figure 1: Abdominal CT indicating a mass lesion of the colon before surgery.

Furthermore, red blood cell lines were hyperproliferative, and clusters of juvenile red blood cells were visible, which were distributed in the trabecular region, and the proportion of the megakaryocytes was normal. The bone marrow biopsy revealed that bone marrow hematopoietic hyperplasia was active and no tumor involving bone marrow was found. Bone marrow routine examination showed that the smear had an active proliferation of nuclear cells without obvious abnormal cells on April 12, 2017. After admission to our department, the patient went to a hospital in Shanghai for pathological consultation based on the data and pathological sections to confirm the diagnosis of the double primary tumor. The result of consultation was the same as that of our hospital. The patient presented significant abdominal pain while waiting for the result of pathological consultation after surgery. CT scan showed obvious abdominal lymphadenopathy, indicating the progression of lymphoma (no CT images because of many enlarged lymph nodes).

According to the principle of dual primary tumor treatment, this patient underwent a radical resection of a tumor in the descending colon cancer in our hospital on March 7, 2017, and postoperative adjuvant chemotherapy was performed to reduce the risk of recurrence and metastasis. Patients with NHL at stage III were mainly treated with internal medicine, and chemotherapy was required because of obvious clinical symptoms. However, there is no chemotherapy scheme for both tumors. In addition, the side effects of two chemotherapy regimens on bilateral tumors are too severe to be tolerated by elderly patients. After discussing the multidisciplinary diagnosis and treatment model (MDT), and actively communicating with the patient's family, MCL with clinical symptoms was treated. R-CHOP chemotherapy regimen was performed for five times, including metrology (600 mg, day 1), dexamethasone (10 mg, days 2-6), pharmorubicin (80 mg, day 2), cyclophosphamide (0.8 g, day 2), and vindesine (4 mg, day 2 q3w). IV degree of the bone marrow was suppressed, and granulocytes were lacking after the first chemotherapy. Following the subsequent chemotherapy, PEGylated recombinant human granulocyte colony-stimulating factor needle was used to prevent leukopenia, and no obvious bone marrow suppression occurred. Abdominal pain was relieved, and abdominal lymph nodes became smaller upon the first chemotherapy. On June 6, 2017, abdominal CT indicated no obvious occupying lesion in hepatic segment IV (Figure 3a). After the fifth course of chemotherapy, abdominal CT was performed on August 30, 2017, and the result showed the hepatic segment IV occupation and metastasis may occur (Figure 3b). Enhanced MRI was performed on September 5, 2017, because the abdominal CT was not clear and the results

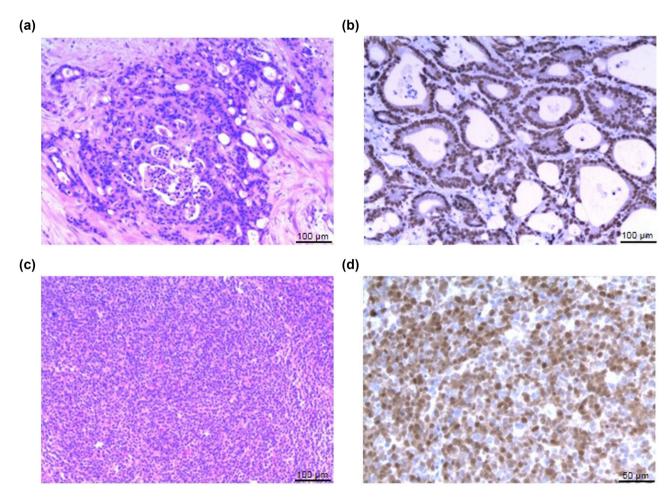


Figure 2: (a) HE staining of postoperative intestinal cancer specimen, original magnification $\times 100$. (b) Positive with CDX-2 ($\times 100$). (c) HE staining of postoperative MCL specimen ($\times 100$). (d) Positive with cyclin D1 ($\times 200$).

revealed obvious occupying lesion in segment IV of the liver and the occurrence of metastasis, but the specific nature and source remain unclear (Figure 3c).

Intrahepatic lesion biopsy, surgery, radiofrequency ablation (RF), stereotactic body radiation therapy (SBRT) and other local treatments were not performed because of the old age of the patient. According to the probability of metastasis of the two tumors to the liver, colon cancer was more likely to metastasize to the liver. In addition, MCL was in remission, and hence, the protocol was made based on the hepatic metastasis of colorectal cancer. Capecitabine tablets (1.5 g, bid, d1–14) were given orally twice (chemotherapy), and the abdominal CT taken on November 21, 2017, revealed that the lesion was enlarged in the liver (Figure 3d). The patient was recommended to undergo liver mass puncture for pathology, but the family requested to continue with the original chemotherapy. However, xeloda was not taken orally for the third time because of the

low platelet level of the patient and the presence of chemotherapy taboos. Then, the treatment was terminated because of the economic reason.

In July 2018, the patient was admitted to our department due to neck swelling, tracheal compression, and dyspnea. The neck ultrasound revealed goiter and compression of trachea and esophagus. Needle biopsy indicated that thyroid was invaded by lymphoma. Furthermore, the immunohistochemical results showed CD3 (–), CD20 (+), PAX-5 (+), CD5 (+), Cyclin D1 (+), BCL-2 (+), CD10 (–), CD56 (–), and Ki-67 (+, about 90%), which are consistent with MCL (Figure 4). R-CHOP chemotherapy regimen was not performed because of the costs. Thus, the patient was treated with glucocorticoids and was discharged after improvement in dyspnea. After that, the patient did not receive any treatment. During the follow-up, we found that the patient died at home in January 2019, and the cause of death was unknown.

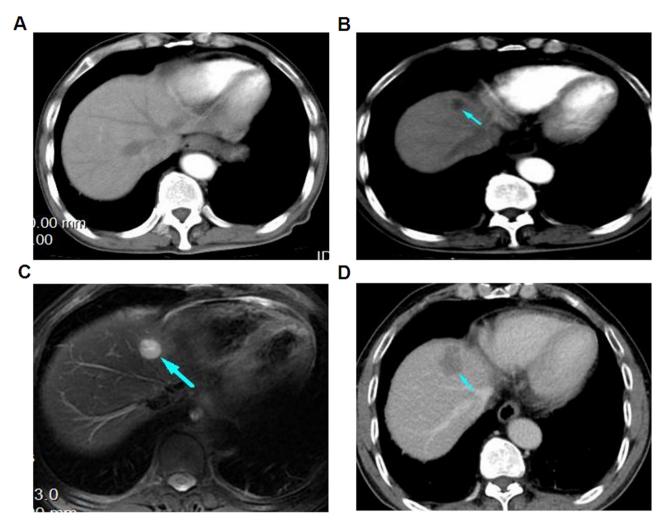


Figure 3: (a) Abdominal enhanced CT revealing no obvious occupying lesion in the hepatic segment IV on June 6, 2017. (b) Abdominal enhanced CT revealing hepatic segment IV occupation and metastasis may occur on August 30, 2017. (c) Abdominal enhanced MRI showing obvious occupying lesion in the hepatic segment IV, and metastasis may occur on September 5, 2017. (d) Abdominal enhanced CT suggesting enlarged hepatic segment IV lesions.

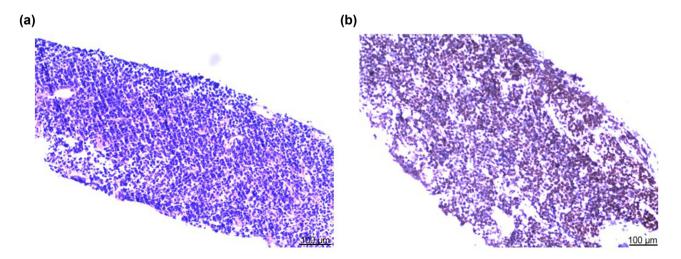


Figure 4: (a) HE staining of fine needle aspiration sample of thyroid $(\times 100)$. (b) Positive with PAX-5 $(\times 100)$.

Ethical statement: The research related to human use has been complied with all the relevant national regulations, institutional policies, and in accordance the tenets of the Helsinki Declaration, and has been approved by the Ethics Committee of Huzhou Central Hospital (20191210-01).

Informed consent: Written informed consent was obtained from the patient for publication of this study and any accompanying images.

3 Discussion

The diagnosis of multiple primary malignancies in the study was performed according to the criteria previously described: each tumor is malignant and has its own unique pathological features; two or more tumors need to be spaced at a normal interval or occur at different sites, but the two are not continuous; and recurrence and metastasis must be excluded [7]. This case showed a combination of colon cancer and MCL, which are two different types occurred simultaneously, thus meeting the criteria for multiple primary malignancy.

In terms of treatment, there is no chemotherapy scheme for both tumors. Currently, the treatment for colon cancer is mostly surgical resection followed by adjuvant chemotherapy [8]. Previous studies have reported that although the first-line treatment for MCL patients is generally considered too toxic for elderly patients, moderate intensive chemotherapy, such as R-CHOP, still remained the best induction regimen for elderly patients with MCL [9]. In this case, according to the principle of dual primary tumor treatment, radical resection of colon cancer and postoperative adjuvant chemotherapy were performed, whereas patients with MCL were mainly treated with internal medicine, and R-CHOP chemotherapy was required because of obvious clinical symptoms. Moreover, oral chemotherapy was also adopted in the patient for the treatment of hepatic and thyroid metastasis.

The pathogenesis of multiple primary malignancies remains unclear. Several researches have reported that risk factors, including low immunity, the existence of tumor-susceptibility genes, mutual signal channels and continuous exposure to toxic and harmful carcinogens, are related with multiple primary malignancy [10–12]. Colon cancer is often associated with endometrial, gastric, and ovarian cancers, but little is reported to its correlations with blood malignancies [13]. It has been reported that the patients underwent secondary breast,

ovarian, and uterine cancers after colorectal cancer in Korea [14]. Liu et al. reported a case with male breast cancer and coexisting MCL in 2017 [7]. Besides, Hu et al. reported that a 74-year-old woman had a history of colon cancer and developed multiple primary malignancies including stomach, lung, breast, and liver cancers [15]. In our study, two types of malignant tumor components (colon cancer and MCL) were noticed simultaneously in the patient, followed by invasion of thyroid by lymphoma. Multiple primary tumor is usually found in the same system or in different parts of the same organ [16]. Colon cancer and coexisting MCL in this case are rare because colon belongs to the parenchymal organ, whereas MCL is a disease of the lymphatic hematopoietic system. The patient was admitted to the hospital because of digestive symptoms, and the colonoscopy revealed colon cancer. Furthermore, abdominal CT showed lymphadenectasis. Lymph node metastasis of colon malignant tumor generally occurs through lymphatic circulation path [17]. Therefore, colon cancer with lymph node metastasis rather than the second primary tumor would be considered when the swollen lymph nodes were observed in imagological diagnosis, resulting in missed diagnosis. In addition, the lymph nodes submitted for examination in the case were colorectal cancer metastasis, and retroperitoneal lymph nodes were MCL. Thus, pathological diagnosis should be performed for the specimens of the lymph node to avoid missed diagnosis. Moreover, auxiliary examination including regional lymph nodes and puncture of mass should be completed before treatment because the liver lesions were not examined for pathology with the unknown nature. As for therapeutic effect, the prognosis of dual primary tumors is worse than that of the corresponding single primary tumors, which may be related to the low immunity of patients and the failure of treatment of both tumors [18–21].

The synchronous of MCL and colonic carcinoma in one patient is rare. Liao et al. [22] previously reported a case of advanced sigmoid adenomcarcinoma and duodenal MCL with the involvement of lymph nodes. This case was considered as extremely rare because the location of MCL was identified 20 months after the chemoradiotherapy of adenocarcinoma. In the case described by Sztarkier et al. [23], there was also a case of adenocarcinoma; however, the MCL was present in tubular adenoma with polyp formation. One polyp was infiltered by the lymphoid cell, whereas two regional lymph nodes were partially replaced by MCL. Handra-Luca [24] has described a patient with intestinal tumors of adenoma-lymphoma without compromising the lymph nodes. All three patients described earlier received R-CHOP regimen after the diagnosis of MCL, which is consistent with our case. Yet, the used drugs and its dosage in R-CHOP regimen were different, which may depend on the patients' clinical situation. Besides, compared with other studies, our study is the first one that has not only introduced a rare case of synchronous of colon cancer and MCL but also provided a clinical guidance of composite tumors to reduce the probability of misdiagnosis.

In conclusion, colon cancer with multiple lymphadenopathy throughout the body (malignant lymphoma was considered) was detected through abdominal CT. Combined with the immunohistochemical results, the patient was diagnosed as synchronous primary malignancy colon cancer and MCL, avoiding missed diagnosis. The diagnosis rate of dual primary tumors is high due to the medical advancements. Doctors require detailed analysis ability and rich clinical experience from multiple disciplines to discuss together before making best choice to formulate the most effective treatment regimen, prolong the survival time of the patients, and improve the quality of life needs to be solved in the future.

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Conflict of interest: The authors have no conflicts of interest to declare.

Data availability statement: The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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