Collision tumor of primary malignant lymphoma and adenocarcinoma in the colon diagnosed by molecular pathology: A case report and literature review

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Abstract

BACKGROUND
Collision tumors of primary malignant lymphoma and adenocarcinoma in the colon are rare. Primary diffuse large B-cell lymphoma (DLBCL)–adenocarcinoma collision tumors are especially rare.

CASE SUMMARY
A 74-year-old woman presented with abdominal pain of 1 mo duration. Biopsy under colonoscopy revealed adenocarcinoma of the ascending colon. Subsequently, the patient underwent laparoscopic radical resection of right colon cancer with lymph node dissection. A collision tumor was found incidentally through postoperative pathological sampling. Genetic analysis showed a collision tumor of DLBCL with germinal center B-cell subtype and TP53 mutation, and adenocarcinoma arising in a tubulovillous adenoma in the colon, with BRAF mutation and mutL homolog 1 promoter methylation. The patient died 3 mo after surgery. To our knowledge, this is the 23rd reported case of collision tumor of colorectal adenocarcinoma and lymphoma. The mean age of the 23 patients was 73 years. The most common site was the cecum. There were 15 cases with follow-up data including 11 Living and four dead with a 3-year overall survival rate of 71.5%.
CONCLUSION

Based on pathological and genetic analysis, surgery combined with chemotherapy or chemoradiotherapy may have good therapeutic effects for collision tumor.

INTRODUCTION

Colorectal cancers (CRCs) are malignant epithelial tumors originating in the large bowel with glandular or mucinous differentiation, and are the second most common cancer in women and the third most common in men[1]. Adenocarcinoma is the most common malignant tumor of the colon, while primary malignant lymphoma is relatively rare. Two or more distinct tumors of different cell lineages that independently occur in the same space or organ and combine to form one mass are defined as collision tumors[1,2]. Collision tumors of primary malignant lymphoma and adenocarcinoma in the colon are rare. To the best of our knowledge, only 22 cases have been described in the literature[3-24]. Here, we report a case of collision tumor of primary diffuse large B-cell lymphoma (DLBCL), not otherwise specified (NOS) with germinal center B-cell (GCB) subtype and TP53 mutation, and adenocarcinoma arising in a tubulovillous adenoma in the colon, with BRAF mutation and mutL homolog 1 (MLH1) promoter methylation. We also present a review of the literature.

CASE PRESENTATION

Chief complaints

A 74-year-old woman presented with abdominal pain of 1 mo duration and was referred to Sun Yat-Sen Memorial Hospital, in March 2018.

History of present illness

She presented with abdominal pain of 1 mo duration.

History of past illness
She mentioned a loss of 8 kg over the previous 6 mo and had anemia. Hypertension was confirmed for many years.

**Personal and family history**
The patient denied any family history of malignant tumors.

**Physical examination**
Upon physical examination, no peripheral lymphadenopathy or hepatosplenomegaly was found. A mass was noted in the right lower quadrant.

**Laboratory examinations**
Blood examination showed an increase in carbohydrate antigen 125, carbohydrate antigen 19-9 level, and a decrease in lymphocyte proportion and count, hemoglobin, and total protein (Table 1). Serum lactate dehydrogenase was elevated (538 U/L, normal 108-252 U/L). Blood detection for syphilis, hepatitis B virus, hepatitis C virus and human immunodeficiency virus was negative or normal.

**Imaging examinations**
Hypertensive heart disease was diagnosed by color sonography. Chest radiography showed no evidence of metastasis in the lung. Contrast-enhanced computed tomography revealed bowel wall thickening with contrast enhancement at the cecum, but no lymph node or organ metastasis and a negative scan of the liver and spleen. Colonoscopy revealed a tumor of the ascending colon, which was confirmed as adenocarcinoma on biopsy.

**FURTHER DIAGNOSTIC WORK-UP**
The patient underwent laparoscopic radical resection of right colon cancer with lymph node dissection.
Pathological analysis was performed on a formalin-fixed section of the intestine with omentum (including ileum, cecum and ascending colon). The lengths of the three portions were 6 cm, 11 cm and 22 cm, respectively; and the circumferences were 2.5 cm, 8 cm and 6 cm. A circumferential ulcerative mass a size of 11 cm × 7.5 cm × 10 cm was seen on the cecal mucosa adjacent to the ileocecal valve (Figure 1). Macroscopically, the mass appeared to consist of two tumors. The cut surface of the mass with crater-like appearance was gray, soft, fish-like, with a necrotic-appearing central area, whereas the remaining polypoid part of the mass was hard and grayish-white. A cross-section demonstrated that these two tumors formed a union, and it was impossible to determine grossly the borderline of the two tumors. Adjacent to the tumor, a 0.6-cm polypoid mass was found in the ascending colon. The appendix was 5 cm long, 0.8 cm in diameter, and the volume of the omentum was 15 cm × 15 cm × 15 cm. Nine lymph nodes varying in size from 0.1 cm to 1.2 cm were isolated from the specimen. Microscopy showed that the tumor had two components that were adjacent to each other but independent (Figure 2). One component was a moderately differentiated adenocarcinoma with a mucinous component arising in a tubulovillous adenoma (Figure 3A), which invaded the muscularis propria with pushing borders (Figure 3B). The other component was distributed from the mucosal lamina to the subserous layer. The medium-to-large lymphocytes grew diffusely, with uniform morphology, frequent mitosis, and obvious atypia (Figure 3C). There was no intramural and extramural vascular, lymphatic or perineural invasion. The surgical cut margins and the appendix were free of tumors and all lymph nodes lacked tumor dissemination. Histological examination of the 0.6-cm polypoid mass in the ascending colon showed a tubular adenoma.

Immunohistochemistry revealed that the adenocarcinoma strongly expressed cytokeratin (CK) (Figure 3D), CK20, caudal-related homeobox transcription factor 2 and mutS homolog 6, but was negative for mutS homolog 2, MLH1 and postmeiotic segregation increased 2. Immunohistochemistry of the atypical lymphocytes was strongly and diffusely positive for paired-box 5, cluster of differentiation 20 (CD20).
(Figure 3E), CD79, CD10, B-cell lymphoma (Bcl)-6, multiple myeloma oncogene-1 and lambda, and negative for kappa, Bcl2, cyclinD1, CD5, CD21, CD23, CD38, CD138, CD3 (Figure 3F), CD56, anaplastic lymphoma kinase, terminal deoxynucleotidyl transferase and CK. The MIB-1 Labeling index was ~80%. Expression of C-myc was detected in 30% of these atypical lymphocytes. P53-positive immunoreactivity was 90%. In situ hybridization was negative for Epstein-Barr virus (EBV)-encoded small RNA. Mutational analysis of BRAF was restricted to the V600E alteration. BRAF mutations were detected from formalin-fixed paraffin-embedded sections using the Snapshot mutation detection platform. MLH1 promoter methylation was performed by quantitative real-time polymerase chain reaction. Adenocarcinoma had BRAF mutation and MLH1 promoter methylation. IgH gene rearrangement study showed that the B-cell rearrangement was positive (polymerase chain reaction + fragment analysis). Fluorescence in situ hybridization of the atypical lymphocytes identified no translocations of IGH/BCL2, IGH/MYC, IGH/CCND1 and no break-apart rearrangement of BCL6. TP53 mutations were found by the AmpliChip p53 Research Test (Roche Molecular Systems), which is a microarray-based assay that detects mutations in exons 2-11.

**FINAL DIAGNOSIS**

The morphological, immunohistochemical and molecular pathological findings confirmed the diagnosis of collision tumor of primary DLBCL, NOS with GCB subtype and TP53 mutation, and adenocarcinoma arising in a tubulovillous adenoma in the colon, with BRAF mutation and MLH1 promoter methylation. The colon adenocarcinoma was staged as T2N0M0 according to the American Joint Committee on Cancer Tumor-Node-Metastasis staging system[25]. Postoperative positron emission tomography-computed tomography scan revealed that there was no metastasis to the lymphoid system or bone marrow, which was confirmed by a bone marrow biopsy. DLBCL was stage IIE with bulky disease, according to the revised staging system for malignant lymphoma based on the Lugano classification[26,27]. The Eastern Cooperative
Oncology Group performance status [28] of the patient was 2. The International Prognostic Index (IPI) of the National Comprehensive Cancer Network [29] score was 5, which indicated that the patient was in the high-intermediate risk of survival group.

**TREATMENT**

The patient underwent laparoscopic radical resection of right colon cancer with lymph node dissection.

**OUTCOME AND FOLLOW-UP**

The symptoms rapidly progressed and the patient died 3 mo after the initial diagnosis of collision tumor of primary malignant lymphoma and adenocarcinoma in the colon.

**LITERATURE REVIEW**

There are few reports of colonic adenocarcinoma in collision with primary colorectal lymphoma [3-24]. The clinicopathological characteristics of the present case and 22 previous cases with collision tumors of primary colorectal lymphoma and adenocarcinoma are reviewed.

This type of tumor mostly occurs in older people. The age of the patients ranged from 43 to 86 years, with a mean of 73 years. Most of the patients were > 60 years old (21/22) and the male-to-female ratio was 1.3 to 1. In all cases, anemia, multiple colon polyps, and inflammatory bowel disease were the most common diseases in past medical history. Most cases had symptoms associated with colorectal adenocarcinoma (20/23). The most common site of lesions was the cecum (7/23). The histological morphology of tumors could be roughly divided into three types [14]. Thirteen cases were in the most common type, which was carcinoma and lymphoma are in the same tumor and the two types of tumor cells are mixed and grow crosswise. Seven cases and our case were in the second type, with carcinoma and lymphoma in the same tumor and independently. Third, the two tumor components are in separate tumors, and the two tumors are adjacent or close to each other.
Most of the adenocarcinoma components were moderately differentiated (18/21), and there were two well-differentiated and one poorly differentiated adenocarcinoma. Among 16 patients with available histopathological staging of adenocarcinoma, there were seven, four, three, one and one in stages I, IIA, IIIB, IIIC and IV, respectively. Three cases showed adenocarcinoma arising in a villous adenoma. There was a large tubulovillous adenoma containing invasive adenocarcinoma in two cases. The most common histological subtypes of the lymphoma were B-cell lymphomas, such as DLBCL (9 cases), and only one case was peripheral T-cell lymphoma. Among 20 patients with an available histopathological staging of lymphoma, there were seven, three and 10 in stages I, II and IV, respectively. Sixteen of 19 patients had an intermediate or high-risk IPI score, and three had a low or intermediate-risk IPI score\textsuperscript{28-31}. Thus, > 50% of cases were stage IV and 84.2% of cases had intermediate or high-risk IPI scores in lymphoma components.

There were 15 cases with follow-up data, including 11 alive and four dead (3 died of malignant lymphoma and 1 of nontumor causes), and survival time ranged from 1 to 48 mo. Three-year overall survival rate was 71.5%. According to Kaplan-Meier survival analysis, the overall survival rate of patients who underwent surgery combined with chemotherapy or radiotherapy was higher than that of surgery alone, although the difference was not significant due to the small sample size (0.8333 vs 0.514). This suggested that adjuvant radiotherapy or chemotherapy combined with surgery had survival benefits. Seven patients underwent surgery alone and six underwent surgery in combination with chemotherapy [4 R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone); 1 FOLFOX (folinic acid, fluorouracil and oxaliplatin) to R-CHOP; 1 FOLFOX]; two received surgery in combination with chemotherapy and radiotherapy (1 R-CHOP; 1 R-CHOP to FOLFOX); and five received R-CHOP chemotherapy only, among eight patients who received chemotherapy. Among three patients who died from malignant lymphoma progression, two underwent surgery alone and one received surgery combined with chemotherapy.
(FOLOFX and R-CHOP). Whether lymphoma was a preference factor in the patient’s prognosis remains unclear, due to the lack of large sample data[6].

DISCUSSION

Collision colorectal adenocarcinoma and lymphoma are rare and only a few cases have been reported in the literature[3-24]. Although rectal magnetic resonance imaging could detect different morphology and signal intensity in each tumor, pathological identification of the two components is the only way to make the correct diagnosis[4, 32]. Pathologists should be aware of the existence of collision tumors for two reasons[4, 8]. The first reason is that the presence of lymphocytes in the vicinity of colonic carcinomas is common, but these cells are not always reactive. A different appearance from that of the other on gross resection specimen and/or an extensive or monotonous infiltrate should alert pathologists to carefully assess its morphology, immunophenotype and clonality to confirm or exclude a coexisting lymphoma. The second reason is any effacement of the architecture of lymph nodes from a resection specimen with a known colonic carcinoma needs a closer look to exclude the possibility of an underlying lymphoma.

Primary colonic lymphoma and adenocarcinoma might be attributed to the advanced age of the patient[8]. The development of DLBCL in one case with a medical history of rheumatoid arthritis was determined to be driven by EBV, with immunosuppression being the underlying cause[24].

Microsatellite instability (MSI) drives one of the key mechanisms of oncogenesis in CRC and the presence of MSI is important in two main scenarios[33]. Firstly, in \textit{BRAF} wild-type cases, MSI confers a good prognosis, and CRCs that are microsatellite stable in the context of \textit{BRAF} mutation usually have poor prognosis. The present case with \textit{BRAF} mutation and mismatch repair (MMR) had survival time of only 3 mo. Drugs targeting the \textit{BRAF} gene may bring hope for the treatment of such collision tumors. Secondly, the presence of MSI is important in the context of cancer immunotherapy. More recently, studies have reported significant responses of MSI cancers (CRCs and others) to
programmed death ligand 1 inhibitor in patients who failed conventional therapy\[34,35\]. In the large intestine, the most common type of lymphoma is DLBCL (> 50%), followed by extranodal marginal zone lymphoma, follicular lymphoma, mantle cell lymphoma and Burkitt’s lymphoma. The incidence of large intestinal lymphoma has increased over the years, attributable to acquired or iatrogenic immunodeficiency\[36\]. Patients with immunodeficiency are more prone to develop lymphoma. Although the influence of one cancer on the other is largely unknown, certain proneoplastic cytokines that are released by tumor cells have paracrine activities\[18\]. One could envision a situation whereby one tumor type is secreting transforming growth factor b, not only cloaking the source tumors but also any adjacent disparate tumors. One tumor type might benefit from its collision counterpart via the stimulation of angiogenesis\[18\]. The loss of MMR and resulting MSI are contributing factors to this association between carcinoma and lymphoid infiltration. The presence of lymphoma may help developing adenocarcinoma evade the immune system\[20\]. Therefore, immunotherapy with MMR benefits both adenocarcinoma and lymphoma. EBV is an established risk factor for lymphoma and may also increase the risk of adenocarcinoma\[7,24\].

A therapeutic dilemma exists in deciding the course of treatment in patients with collision adenocarcinoma and lymphoma\[5\]. There is agreement that surgical treatment alone is effective for localized disease, while combined chemotherapy is the mainstay for disseminated disease. The treatment of collision tumors requires simultaneous treatment of the two tumor components; mainly surgical resection combined with radiotherapy and chemotherapy\[15\]. For the adenocarcinoma component, if it is well-differentiated, there is no need to perform radiotherapy and chemotherapy for cancer after resection. If there is lymph node or even distant metastasis, adjuvant radiotherapy and chemotherapy can be carried out after surgery if the physical condition allows. For the lymphoma component, the corresponding radiotherapy and chemotherapy regimen is added according to the different subtypes. However, the order of treatment can be a source of debate because it has not been established which tumor should be treated first\[16\]. Although three of 23 cases died due to malignant lymphoma, there have been so
few reports of cases with collision tumors composed of both neoplasms that it has not been possible to confirm whether lymphoma was a preference factor in prognosis[8]. It is inferred that the prognosis of patients with collision tumor depends on the more aggressive histological grade and stage of the two collision components, and is also closely related to comprehensive and appropriate treatment[15].

**CONCLUSION**

Based on pathological examination and genetic analysis, surgery combined with dose-adjusted chemotherapy or chemoradiotherapy may have good therapeutic effects for collision tumor of lymphoma-adenocarcinoma, but additional case studies are needed for confirmation.
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