SPANDIDOS PUBLICATIONS

ONCOLOGY LETTERS 11: 2801-2805, 2016

Collision tumor consisting of primary follicular lymphoma and adenocarcinoma in the cecum: A case report and literature review

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Received February 18, 2015; Accepted February 4, 2016

DOI: 10.3892/ol.2016.4310

Abstract. The present study reports the case of a collision tumor consisting of follicular lymphoma (FL) and adenocarcinoma in the cecum of a 73-year-old man. To the best of our knowledge, the present study is the 11th case of a collision tumor consisting of colon adenocarcinoma and lymphoma to be reported in the literature, and the first case of cecum adenocarcinoma with low grade FL in the same segment of the cecum and the same regional lymph node to be reported. The present study reviewed the literature to determine treatment options for patients with collision tumors. The present patient was administered with adjuvant chemotherapy for T3N1M0 colon cancer following surgery, due to the dominance of colon adenocarcinoma in the collision tumor. Following the completion of treatment, progression of the untreated FL was observed. In the literature, patients with collision tumors are administered with chemotherapy for stage IV FL, and following the completion of treatment patients have presented with a recurrence of early stage colon adenocarcinoma. The recommended treatment for collision tumors is dependent on the dominant tumor; however, the treatment options for collision tumors in the literature appeared to exacerbate the other tumor. The characteristics of the tumors altered following chemotherapy, and immunological alterations in the tumors due to chemotherapy appear to have contributed to the exacerbation of the tumors. Therefore, patients with early-stage tumors should be considered at risk of recurrence of other malignancies, which are present in collision tumors.

Introduction

Colorectal cancer is the fourth most frequently diagnosed cancer in the USA (1). Primary colonic lymphoma is rare, accounting for 0.16-0.60% of all primary colorectal cancers and 10-20% of all gastrointestinal lymphomas (2). The most frequent location of colonic lymphoma at diagnosis is the ileocecal region (2-4). Follicular lymphoma (FL) is the most common subtype of indolent non-Hodgkin's lymphoma (NHL) and the second most common type of gastrointestinal lymphoma (5). Collision colorectal adenocarcinoma and lymphoma are extremely rare and only a few cases have been reported in the literature (6-12). Lymphoma is frequently characterized by chromosomal translocations and certain genetic aberrations, and its growth and development into a malignant neoplasm is dependent on its ability to escape natural host defenses (13). Chemotherapy may cause the patient to develop an immunocompromised status (13), and immunosuppression is known to play a role in the pathogenesis of lymphoma and therefore may be involved in the pathogenesis of collision tumor (14,15). The present study reports the case of a patient with a collision tumor of primary follicular lymphoma and adenocarcinoma, located in the cecum. Following adjuvant treatment of colon carcinoma, the low grade lymphoma demonstrated an unexpected aggressive course. Therefore, it is possible that receiving chemotherapy for the treatment of one type of tumor may trigger the progression of the other type of cancer in collision tumors.

Case report

A 73-year-old male was referred to Gaziantep University Hospital (Gaziantep, Turkey) in August 2013 with a history of muscle weakness, fatigue, weight loss and colic abdominal pain for the previous 2 months. A physical examination revealed that the right side of the lower abdomen of the patient was painful, but there was no lymphomegaly or hepatosplenomegaly. Laboratory tests demonstrated that the patient possessed a hemoglobin level of 9.9 g/dl (normal range, 11.2-15.7 g/dl), white blood cell count of 12,300 cells/μl [normal range, 3,980-10,040; neutrophils, 85% (normal range, 34-71%); lymphocytes, 9.0% (normal range, 19.3-51.7%); monocytes, 4.1% (normal range, 4.4-12.5%)], platelet count of 356,000 cells/μl (normal range, 182,000-369,000 cells/μl), lactate dehydrogenase (LDH) level of 255 units/l (normal range, 125-247 units/l), erythrocyte sedimentation rate (ESR) of 55 mm/h (normal range, 1-20 mm/h) and carcinoembryonal

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Key words: collision tumor, colon cancer, follicular lymphoma, immune system

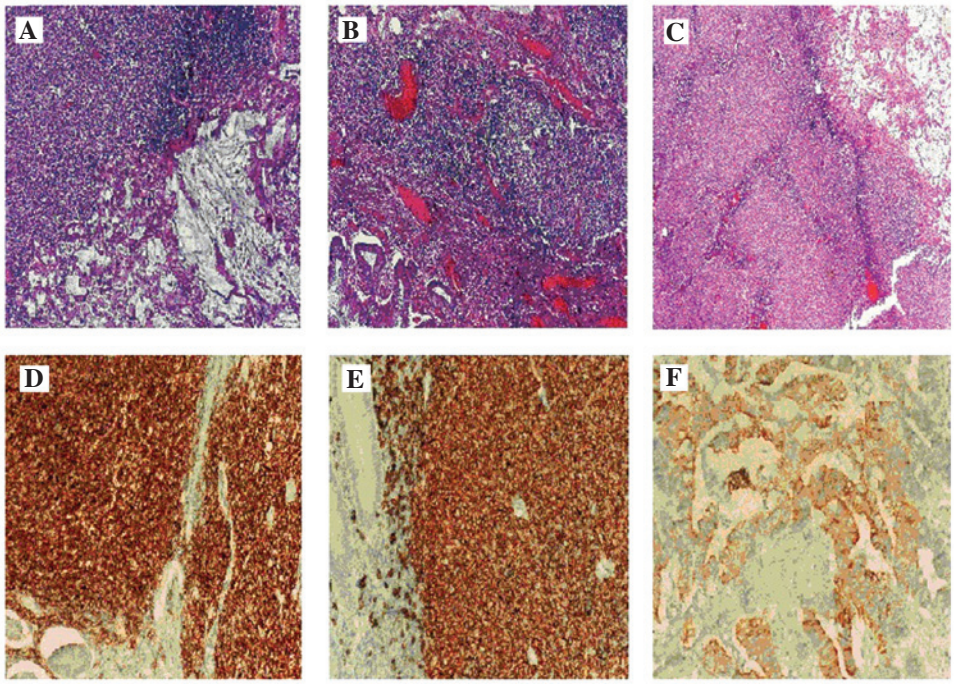

Figure 1. Photomicrographs demonstrating the presence of collision sections of adenocarcinoma and lymphoma in the (A) lymph node (stain, H&E; magnification, x100) and (B) cecum as mucin rich atypical glands and follicular lymphoma (stain, H&E; magnification, x100) and the (C) lymph node (stain, H&E; magnification, x40). Immunohistochemical staining revealed (D) CD10 positivity (magnification, x200) and (E) CD20 positivity (magnification, x200) in the lymph node and (F) pancytokeratin positivity in the adenocarcinoma component of the cecum (magnification, x200). CD, cluster of differentiation. H&E, hematoxylin and eosin.

antigen (CEA) level of 2.8 ng/ml (normal range, 0-3.0 ng/ml). Abdominal computed tomography revealed the presence of a 8-cm mass located in the cecum of the patient. A preliminary diagnosis of an abscess was made, however when the patient underwent a laparotomy, the mass was observed to be tumorous. A right hemicolectomy with lymph node, adjacent omentum and intestine dissection and an appendectomy was performed. An ulcerovegetant mass ~4 cm in diameter at the ileocecal valve was detected. Macroscopically, the tumor appeared to exceed the serosa and extend to the appendix. The pathology results provided a diagnosis of adenocarcinoma and grade 1 FL in the cecum, with metastasis to 1 out of 6 regional lymph nodes. Immunohistochemical analysis, using a light microscope (E600; Nikon Corporation, Tokyo, Japan) supported this diagnosis (Fig. 1), as the adenocarcinoma tissue expressed pancytokeratin (detected by mouse anti-human monoclonal cytokeratin cocktail antibody; cat. no. 313M-18; ready to use; Sigma-Aldrich, St. Louis, MO, USA), and the FL tissue expressed cluster of differentiation (CD)-20 (detected by rabbit anti-human monoclonal CD20 antibody; cat. no. 120R-18; ready to use; Sigma-Aldrich), B-cell lymphoma-2 (Bcl-2; detected by rabbit anti-human monoclonal Bcl-2 antibody; cat. no. 226R-28; ready to use; Sigma-Aldrich) and CD10 (detected by mouse anti-human monoclonal CD10 antibody; cat. no. 110M-18; ready to use; Sigma-Aldrich), but did not express CD3 (detected by rabbit anti-human monoclonal CD3 antibody; cat. no. MRQ-39; ready to use; Sigma-Aldrich), CD5 (detected by rabbit anti-human monoclonal CD5 antibody; cat. no. 205R-18; ready to use; Sigma-Aldrich), cyclin D1 (detected by rabbit anti-human monoclonal cyclin D1 antibody; cat. no. 241R-18; ready to use; Sigma-Aldrich) and CD23 (detected by rabbit anti-human monoclonal CD23 antibody; cat. no. 123R-18; ready to use; Sigma-Aldrich). Sections were stained using the ultraView Universal DAB Detection kit (Ventana Medical Systems, Inc., Tucson, AZ, USA) in an automated slide processing system (BenchMark ULTRA; Ventana Medical Systems, Inc.). The colon carcinoma was staged as T3N1M0 according to the American Joint Committee on Cancer Tumor-Node-Metastasis staging system (16). The post-operative positron emission tomography-computed tomography (PET-CT) scan demonstrated the presence of a hypermetabolic lesion [standardized uptake value (SUV), 8.5] located in the right lower abdomen (Fig. 2A). The lesion was diagnosed as an abscess formation due to numerous neutrophils and pus identified by aspiration biopsy. At follow-up 2 weeks subsequent to surgery, the abscess had regressed due to aspiration and antibiotherapy for 14 days (1 g meropenem, 3 times daily; 500 mg metronizadole, 3 times daily). PET-CT revealed that there was no metastasis to the lymphoid system or bone marrow, which was confirmed by a bone marrow biopsy.

The FL of the patient was stage 1EA, according to the Ann Arbor staging system (17), and the Follicular Lymphoma International Prognostic Index (FLIPI) (18) score was 2, which indicated that the patient was in the intermediate-risk of survival group. The Eastern Cooperative Oncology Group (ECOG) performance status of the patient was 0 (19). The treatment of the patient was coordinated in October 2013 following stabilization of the abscess. The adjuvant chemotherapy administered to the patient consisted of 5-fluorouracil (2,000 mg/m^2 on days 1 and 15) with leucovorin

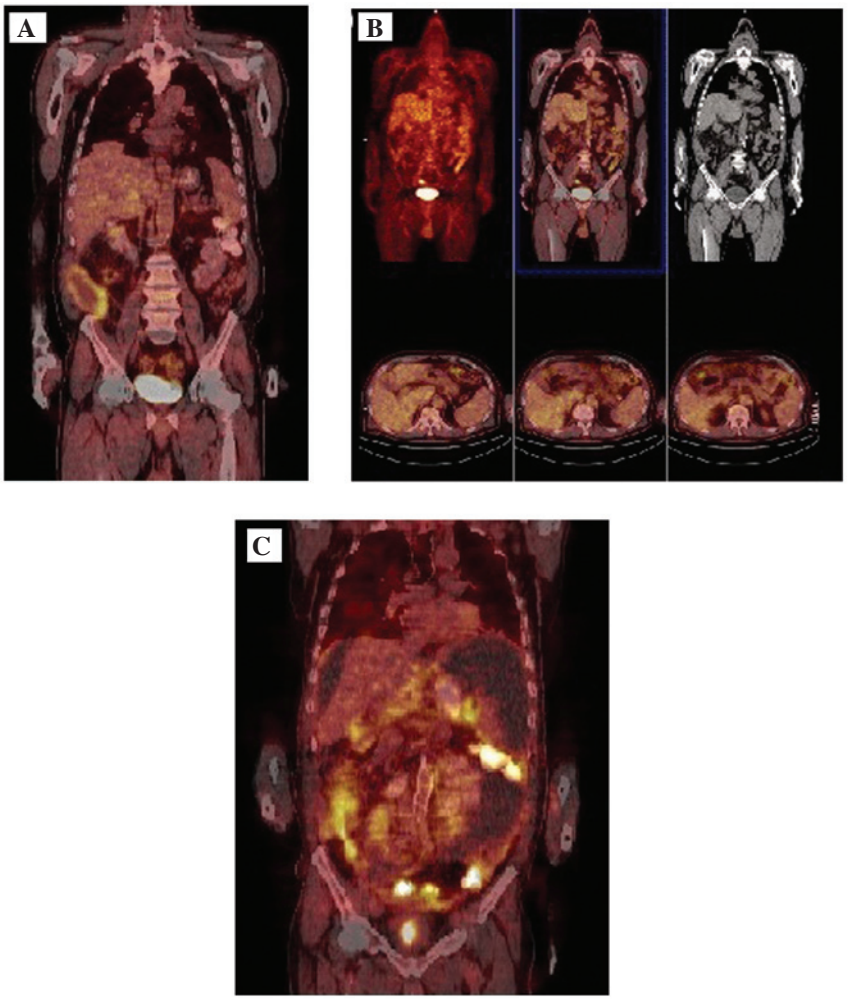

Figure 2. (A) Post-operative PET-CT scan demonstrating the presence of a hypermetabolic lesion in the right lower abdomen. (B) PET-CT scan demonstrating the presence of hypermetabolic lymph nodes in the abdomen. (C) Extensive peritoneal involvement following treatment for follicular lymphoma. PET-CT, positron emission tomography-computed tomography.

and oxaliplatin (85 mg/m^2 on days 1 and 15) (FOLFOX-4) for 28 days in 6 cycles. Following 6 cycles of FOLFOX-4 chemotherapy, the patient presented with abdominal pain, and on physical examination it was observed that the patient exhibited shifting dullness on percussion indicating ascites. A PET-CT scan revealed novel SUVs in the hepatic (SUV, 3.3), paraaortic (SUV, 2.9) and peripancreatic lymph nodes (SUV, 2.8) and in the ascending colon (SUV, 6.1; Fig. 2B). Laboratory tests revealed that the patient possessed a hemoglobin concentration of 10.8 g/dl, white blood cell count of 6,500 cells/μl, platelet count of 153,000 cells/μl, LDH level of 320 units/l, ESR of 80 mm/h and CEA level of 2.5 ng/ml. The ascites possessed malignant features, which confirmed that the lymphoma had progressed. The patient did not exhibit stage B symptoms and was staged as 2EA FL using the Ann Arbor staging system. The ECOG performance status of the patient increased to 2. Consequently, chemotherapy was administered to the patient, which consisted of cyclophosphamide (750 mg/m^2 on day 1), vincristine (1.4 mg/m^2 on day 1), prednisolone (100 mg on days 1-5) and rituximab (375 mg/m^2 on day 1) once every 3 weeks. The symptoms of the patient rapidly progressed and the patient succumbed to the cancer 2 months subsequent to the initiation of treatment.

Discussion

NHL is the most common hematological malignancy, consisting of a heterogeneous group of neoplastic disorders (20). The pathogenesis of lymphoma results from a combination of acquired somatic mutations, leading to defects in the antitumor immunity of the patient and the local microenvironment of the tumor (13). The progression of lymphoma depends on various factors, including the age and immune status of the patient (21). For the optimal management of lymphoma, the medical history, ECOG performance status and symptoms of the patient, history of lymphoma, including if the tumor was indolent or aggressive, long-term outcome (curative or palliative) and B cell or T cell origin of the tumor, and stage of the disease are notable features. Indolent B-cell lymphomas are characterized by a relapsing and remitting course (22). Treatment should be decided by considering the grade, stage and symptoms of the disease. FL is the most common subtype of indolent NHL and accounts for 22% of newly diagnosed NHLs (21). Intermittent chemo therapy is provided to control the symptoms of the disease, but this is not curative in the majority of cases. Clinical observation, also termed watchful waiting, is an important

strategy for asymptomatic patients with a low tumor burden, since spontaneous remission occurs in 8-10% of patients, as a lack of curative therapy and an insufficient result of early treatment has not improved the survival rate of patients. The risk of FL developing into a more aggressive disease in untreated indolent lymphomas is 20% at 5 years and 30% at 10 years (23).

FL possesses a t(14;18) (q32;q21) translocation, which is observed in 80-90% of patients and leads to the Bcl-2 oncogene becoming under the control of the immunoglobulin H locus, which leads to impaired cellular apoptosis (24). Immunohistochemical analysis is used for the determination of immonophenotype, and flow cytometry is used for cell surface marker analysis. FL has a characteristic immunophenotype, which is $CD20^+$, $CD10^+$ and $Bcl\text{-}2^+$. While grade 1 and 2 FLs exhibit an indolent clinical behavior, grade 3 FL resembles a large diffuse B-cell lymphoma. Currently, involved site radiation therapy (ISRT) is the standard treatment for stage 1 or 2 low-grade FL, and patients that were initially treated with radiation therapy (RT) have a median overall survival time of ~14 years (25). According to previous studies, if the tumor burden is low the preferred management of FL is RT or clinical observation; however, if the tumor burden is high or abdominal disease is present, rituximab with or without chemotherapy is advised (25,26).

The present study reviewed collision tumor cases from the literature and identified little information concerning a treatment option for collision tumors. Lin *et al* (11) reported the case of a patient with T3N1aM1 colon cancer and low-grade lymphoma, who received oxaliplatin chemotherapy with leucovorin and 5-fluorouracil (FOLFOX-6) chemotherapy for 6 cycles, followed by capecitabine for 24 months for the treatment of colon cancer. Chemotherapy was continued due to suspicion of metastases in the lungs, however, lymphoma did not recur during the 24-month follow-up. In addition, Sasaki *et al* (10) reported the case of a patient with T3N0M0 colon cancer and stage IV FL, who received 6 courses of combined chemotherapy, consisting of cyclophosphamide, doxorubicin, vincristine and prednisone regimen with rituximab, for the treatment of FL. Malignant lymphoma was dominant in this case and the initial systemic chemotherapy was administered for malignant lymphoma, and a complete response was obtained. However, there were multiple liver metastases of colon adenocarcinoma present, despite the early stage of disease.

The present patient was diagnosed with stage 1EA and grade 1 FL and was considered to belong to the intermediate-risk group, according to the FLIPI score. Therefore, the T3N1M0 colon cancer was considered to require treatment priority. Slow disease progression is expected in grade 1 and stage 1 FL; therefore, a watchful waiting strategy or local RT appeared to be a reasonable management alternative for the present patient in the early stages of FL. However, the progression of lymphoma developed unexpectedly and rapidly within 6 months. The patient presented with a stage IIEA symptomatic lymphoma progression, consisting of massive abdominal lymphadenopaties and massive ascites (Fig. 2C). The immunodeficiency effect of colon cancer chemotherapy may explain the progression of FL, which is usually estimated to not occur for a long time. Consequently, a reassessment of the present case suggests that the addition of ISRT for FL with adjuvant colon cancer treatment may have been an appropriate treatment option for the present patient.

The association between the immune system and cancer development has been previously well described (27). This association may explain the pathogenesis of the collision tumor and premature recurrence of FL in the present case. The present study demonstrated the challenges in deciding the optimal therapy for collision tumors and highlights the importance of close follow-up for the two tumors during treatment. Previous studies have limited data recommending convenient treatment and follow-up strategies; therefore, novel cases of patients with collision tumors in the literature may provide additional information concerning optimal treatment approaches and the prognosis of these patients.

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