A Case of Multiple Primary Cancer with Follicular Lymphoma

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The incidence of multiple primary cancer (MPC) is low but has been reported occasionally. Although follicular lymphoma is rare in Korea, the incidence is reported to be gradually increasing. We report a case of synchronous and metachronous MPC consisting of esophagus (squamous cell carcinoma), stomach (adenocarcinoma), and ampulla of Vater (extranodal follicular lymphoma grade 1) in a patient diagnosed as follicular lymphoma (grade 3a) six years ago. In a complicated case like ours, concurrent therapeutic control of synchronous MPC and metachronous hematological malignancy is challenging; meticulous examination and prioritized target therapy are essential for patients’ survival. (Korean J Helicobacter Up Gastrointest Res 2014;14:61-66)

Key Words: Multiple primary cancer; Squamous cell carcinoma; Adenocarcinoma; Follicular lymphoma

INTRODUCTION

Multiple primary cancer (MPC) is defined as the occurrence of two or more primary cancers arising in separate organs without possibility of metastasis or different histologic cancers arising in one organ. MPC was first introduced by Billroth in the late 19th century and Warren and Gates1 published a literature review of 1,259 cases reported worldwide. Afterward, Moertel et al.2 classified MPC into three categories and reported an incidence of MPC of 2.8% of all cancers. The incidence of MPC in Korea has been reported as 0.7∼3%.3

In Korea, cases of MPC involving esophagus and lung, esophagus, stomach, and liver and gastric adenocarcinoma and diffuse large B cell lymphoma have been rarely reported.4,5 In particular, cases of solid MPC accompanying hematologic malignancy are even rarer.

We report on the case of a patient who was previously diagnosed and treated for follicular lymphoma six years ago, who presented with dysphagia: a mass in the esophagus, stomach, and ampulla of Vater was observed on gastro-duodenoscopy and pathologically confirmed as esophageal squamous cell carcinoma, gastric antral adenocarcinoma, and follicular lymphoma grade 1 of the ampulla of Vater.

CASE REPORT

A 66-year-old male who visited for progressive dysphagia was admitted. The patient was diagnosed as diffuse large B cell lymphoma by biopsy of a right cervical mass six years ago (Fig. 1). The patient had progressive high risk disease with clinical stage III; and international prognostic index (IPI) score of 4, as the patient had thoracic, abdominal, and para-aortic lymph node enlargement without bone marrow or gastrointestinal involvement. After six cycles of R-CHOP (rituximab, cyclophosphamide, hydroxydaunorubicin, oncovin, prednisone) chemotherapy, PET showed progression of disease and the patient received an additional three cycles of second line DHAP (cisplatin, cytosine, arabinoside, dexamethasone) chemotherapy, PET showed progression of disease and the patient received an additional three cycles of second line DHAP (cisplatin, cytosine, arabinoside, dexamethasone) chemotherapy and evaluation afterward showed partial response. The patient collected auto-peripheral blood stem cells for auto-peripheral blood stem cell transplantation for cure; however, his management was lost for five years. In addition, the patient had no symptoms for five years.

Afterwards, the patient revisited with both an inguinal lesion and a left axillary lesion mass for five months and the previously noted cervical mass was not found. Biopsies of inguinal and axillary masses showed follicular lymphoma, grade 1∼2. Due to difference in diagnosis of
follicular lymphoma with previously diagnosed diffuse large B cell lymphoma, the pathologic department reviewed the past tissue, and the final diagnosis of tissue six years ago was changed to follicular lymphoma, grade 3a. Although progression of abdominal and thoracic lymph nodes was found from six years ago, grade of follicular lymphoma dropped from 3a to 1~2. Because the patient had no related symptoms, we decided on observation without treatment of follicular lymphoma.

The patient had no history of smoking or drinking and no specific familial history. Vital signs showed blood pressure of 120/80 mmHg, heart rate of 70 beats/min, respiration rate 20/min, and body temperature 36.5°C. A palpable mass was noted at the left axillary and both inguinal lesions, but not in the cervical lesion. No other abnormality was detected on physical examination. Initial peripheral blood test showed hemoglobin 12.5 mg/dL, white blood cell count 5,530/mm³, platelet 192,000/mm³, erythrocyte sedimentation rate (ESR) 109 mm/hr and LDH 865 IU/L, and levels of AFP, CA19-9, and CEA were normal.

He was examined by endoscope due to dysphagia and the fact that endoscopy could not pass through the ulcerofungating mass measuring approximately 5 cm in size, from 29 cm to 34 cm from the incisor (Fig. 2A). Transnasal endoscopy showed a mass measuring approximately 2.5 cm in size (Fig. 3A) at the posterior wall of the gastric antrum and mass (Fig. 4A) at the ampulla of Vater. Biopsies were performed for each lesion and histologic features confirmed a diagnosis of squamous cell carcinoma in the esophagus (Fig. 2B), adenocarcinoma in the gastric antrum (Fig. 3B), and follicular lymphoma in the ampulla of Vater (Fig. 4B). In immunohistochemical analysis, atypical cells were positive for cluster of differentiation (CD) 20, CD 10, Bcl-2, and Bcl-6, suggesting follicular lymphoma, grade 1.

PET showed increased F-18 fluorodeoxyglucose (FDG) uptake at the mid-esophagus, gastric antrum, cervical and abdominal lymph nodes, and spine. FDG uptake in cervical, abdominal lymph node, and spinal invasion was suspected by invasion from follicular lymphoma. Grade of follicular lymphoma was 1~2, a relatively stable state compared with six years ago.

Concurrent surgery for esophagus and stomach was considered, however, as the patient refused surgery, we decided to treat esophageal cancer first, which mainly affects survival and quality of life. Due to indolent status of follicular lymphoma, we decided to observe the patient.
without treatment. Our patient was in the process of concurrent chemoradiotherapy (CCRT) for advanced esophageal cancer first and masses of esophagus and stomach decreased dramatically after the third cycle CCRT (Fig. 5). We planned on removal of the antral mass by endoscopic submucosal dissection (ESD). However, the patient expired suddenly due to rapid progression of pneumonia during the fifth cycle of chemotherapy (Fig. 6).

**DISCUSSION**

MPC is defined as the occurrence of two or more dif-
different types of cancers arising separately in one patient. Generally accepted diagnostic criteria (Warren and Gates\(^1\)) for MPC are as follows: 1) each cancer should be pathologically confirmed, 2) each histologic aspect of cancers should be different, 3) possibility of metastasis between cancers should be excluded.

Moertel et al.\(^2\) further classified MPC into three groups: group 1 includes two or more primary cancers arising in the same organ or the same histologic cancer arising in bilateral organs, group 2 includes multiple cancers arising in different tissue or organs, and group 3 includes cases that are a mix of groups 1 and 2.

Besides these classifications, cancer can be classified as synchronous and metachronous cancer according to the time interval of cancer development. Differential criteria for synchronous and metachronous cancer is time interval between cancer development greater than six months, and metachronous MPC is defined as a different cancer newly arising after six months of cure of one cancer.\(^6\)

Follicular lymphoma, the most common non-Hodgkin’s lymphoma in the United States of America, comprises approximately 25~40% of non-Hodgkin’s lymphoma cases in western countries; however, it is rare in Korea, comprising only 3% of all non-Hodgkin’s lymphoma. World Health Organization (WHO) grades follicular lymphoma according to 1, 2, 3, based on the number of centrocytes.\(^7\)

According to Kiel classification, follicular lymphoma grade 3, high grade centroblastic lymphoma, is further classified into 3a and 3b by molecular biology, immunohistology, and cytogenetics.\(^8\) There are no specialized treatment guidelines for each grade 3a, 3b, but follicular lymphoma, grade 3, should be treated as a high risk group. However, Conconi et al.\(^9\) recently reported on the possibility of histologic transformation of indolent lymphoma, like that of low grade follicular lymphoma, grade 1\(~2\), and in follicular lymphoma, histologic transformation to diffuse large B cell lymphoma occurs after 10 years in approximately 15% of cases. In particular, a key risk factor for histologic transformation into higher grade lymphoma is rituximab treatment, and a ‘watch and wait’ treatment plan is important in prevention of malignant histologic transformation in cases with low grade follicular lymphoma.

In our case, a patient with follicular lymphoma, grade 3a was misdiagnosed as diffuse large B cell lymphoma six years ago. Follicular lymphoma, grade 3a and 3b, a high grade and high risk lymphoma, is often misdiagnosed as diffuse large B cell lymphoma, however, treatment is the same with rituximab based chemotherapy. Consideration of recurrence after cure of follicular lymphoma six years ago is appropriate, considering that the patient had survived without specific symptoms for six years after treatment of a progressive high grade tumor of follicular lymphoma, grade 3a, stage III, IPH score of 4. However, the possibility of secondary cancer due to loss of follow up for six years cannot be completely excluded. In addition,
follicular lymphoma can slowly wax and wane, taking a benign course. Secondary neoplasm refers to any of a class of cancerous tumors that is either a metastatic offshoot of a primary tumor, or an apparently unrelated tumor that increases in frequency following certain cancer treatments such as chemotherapy or radiotherapy.

According to Moertel et al.'s classification, our case can be classified as group 2 with synchronous dual cancer and metachronous triple cancer. However, as the patient was lost to follow up for six years, there is still a possibility of secondary cancer, not being metachronous triple cancer. In our case, histologic result of inguinal and axillary lesion found five months ago was follicular lymphoma, grade 1~2, and a newly developed ampulla of Vater mass was confirmed as follicular lymphoma, grade 1. In our case, histologic transformation to higher grade lymphoma after treatment with rituximab was not observed and grade of follicular lymphoma dropped from high grade 3a to low grade 1~2. Biopsy of lesions with increased FDP uptake in thoracic and abdominal lymph node and spine was not performed and further careful observation of follicular lymphoma is needed.

Although MPC is rare, its incidence has shown a recent increase due to an increase in the older population, as well as development of diagnostic techniques and cancer treatment methods. In esophageal cancer, coexistence with head and neck cancer has been well studied, and, although rare, it is often found simultaneously with stomach cancer, colorectal cancer, hepatic cancer, breast cancer, malignant lymphoma, and renal cancer. In malignant lymphoma, coexistence with stomach or colon cancer has been well studied: one study conducted in Japan reported that 3.3% of malignant lymphoma coexisted with adenocarcinoma.

Pathogenesis of MPC is known to have a genetic cause, like breast cancer (BRCA)-1, BRCA-1, leading to breast and ovary cancer, infection and immunologic cause, like Kaposi's sarcoma or non-Hodgkin's lymphoma, and environmental or habitual cause, like head and neck, esophageal, and respiratory cancer, however, exact pathogenesis or causes are not yet known.

Treatment guidelines for MPC have not yet been established. Precise pathologic diagnosis of primary cancer and differentiation from metastatic secondary cancer is important in making treatment plans and deciding on prognosis. However, in cases like ours, establishment of treatment plans is not easy due to difficulty in diagnosis of primary cancer in cases with many MPCs and uncertainty regarding whether it is metachronous MPC or metastatic secondary cancer.

Establishment of radical treatment plans for each cancer is recommended when new cancers are diagnosed during follow up after treatment of one cancer. If multiple cancers are diagnosed at one point, a treatment plan should be established according to the type of cancer, susceptibility for treatment, and condition of patient, and, above all, life threatening cancer should be treated first.

In our case, concerning the above mentioned points, we attempted to treat esophageal cancer, which was directly connected with quality of life and survival. Gastric antral cancer measuring approximately 2.5 cm in size accompanying an ulcer was diagnosed as moderate differentiated adenocarcinoma and was impossible to remove endoscopically. The initial plan was to perform simultaneous surgical removal of esophageal and stomach cancer, however, the patient refused and treatment with CCRT was started for esophageal cancer. Further treatment plans for gastric antral adenocarcinoma should be decided with the patient later, and treatment of follicular lymphoma should be decided after careful observation. If the patient had refused an operation ever afterward, we would have attempted to remove gastric cancer by ESD because of a decrease in size after CCRT. Unfortunately, the patient expired due to rapid progression of pneumonia. The cause of rapid deterioration of pneumonia was estimated to be an immune-compromised state during CCRT.

Aggressive surgical treatment of MPCs can improve patient's survival and prognosis of MPCs is not poor. Successful results of surgery for treatment of dual metachronous or synchronous cancers of esophagus and stomach have been reported. Similar to our case, a case of synchronous triple primary cancer that arose in esophagus, stomach, and duodenum, in order, with diagnosis of an esophageal lesion as squamous cell carcinoma and both stomach and duodenum lesions as adenocarcinoma was reported in Korea; however, in our case, all cancers differed in type. In Japan, some cases of surgery for
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