

Metachronous Mantle Cell Lymphoma with a Leukemic Presentation in a Patient with Early Gastric Cancer: A Case Report

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We report here on a case of metachronous second primary non-Hodgkin's lymphoma (NHL) that was diagnosed 6 years after performing subtotal gastrectomy for treating early gastric cancer (EGC). The sub-type analysis revealed mantle cell lymphoma (MCL) of the blastic variant with a leukemic presentation, which was composed of mixed small and medium-sized cells. The immunohistochemical staining for cyclin-D1 was positive. The cytogenetic study revealed t(4;6). In Korea, the risk of developing a second primary cancer following gastric cancer was reported to be less than 3.4%, and NHL comprised less than 6.3% of this second primary cancer. Furthermore, MCL represents about 2% of all lymphomas in Korea. To the best of our knowledge, this is the first report of metachronous primary MCL with a leukemic presentation following curative resection of EGC. (*Korean J Hematol* 2008;43:247-252.)

Key Words: Gastric cancer, Metachronous second primary neoplasms, Mantle cell lymphoma, Leukemia

INTRODUCTION

During the past two decades, the survival rate of patients with gastric cancer has improved significantly, and this led to an increased incidence of second primary cancers. The risk of developing a second primary cancer following gastric cancer was reported less than 3.4% in Korea, and significantly elevated risks were observed for cancers of the colorectum, lung and liver. The non-Hodgkin's lymphoma (NHL) comprised less than 6.3% of second primary cancers following gastric cancer, and about 25~40% of the NHL cases

were considered to be metachronous.^{1,2)}

In this article, we report a case of metachronous second primary mantle cell lymphoma (MCL) of the blastic variant with a leukemic presentation that occurred 6 years after subtotal gastrectomy for early gastric cancer (EGC). In Korea, MCL, a B-cell lymphoma, represents about 2% of lymphomas. Furthermore, MCL with leukemic presentation is extremely rare. To the best of our knowledge, this is the first report of MCL with leukemic presentation as a second primary malignancy following curative resection of EGC.

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CASE REPORT

A 64-year-old male patient was referred to a university hospital in January 2000 for further evaluation of suspicious EGC. Gastric fibroscopy revealed slightly elevated lesion located in posterior wall of antrum of the stomach, and tissue biopsy revealed adenocarcinoma with moderate differentiation. Subtotal gastrectomy with Billroth-I anastomosis was carried out. The tumor was 4×4 cm in size, and it extended to muscularis mucosa without lymph node metastasis (T1N0M0). EGC with IIB+IIC type was pathologically confirmed. He had been in symptom-free state until February 2006 when he complained of postprandial epigastric pain. Gastric fibroscopy showed negative. In May 2006, the abdominopelvic CT scan for evaluation of the periumbilical pain showed multiple enlarged lymph nodes in porta hepatis, portocaval and retroperitoneal space, and the PET-CT scan showed increased FDG uptake in the axial skeleton of whole body, liver, spleen and

multifocal lymph nodes (Fig. 1). Clinical diagnosis of relapsed gastric cancer was made. He refused further evaluation and visited Integrative Cancer Center, Kyung-Hee University for herbal medication in July 2006.

At initial evaluation, there was a significant weight loss of 4~5kg over one month. The peripheral blood showed WBC 2,900/ μ L, hemoglobin 11.3g/dL, hematocrit 33.4%, MCV 94.1fL, platelet 92,000/ μ L, neutrophil 24.0%, band 3.0%, monocyte 5.0%, eosinophil 1.0%, immature cell 67% and reticulocyte 2.5%. The serum levels of uric acid (12.3mg/dL) and β 2-microglobulin (5.7 mg/L) were increased. The serum levels of CEA, CA 19-9, and CA72-4 2.2 were within normal limits.

The gastric fibroscopy showed no evidence of tumor. The neck and chest CT scan showed some enlarged lymph nodes in supraclavicular fossa, anterior mediastinal and bilateral paratracheal area. The abdominopelvic CT scan showed splenomegaly and multiple lymph nodes in the hepatic artery, retropancreatic, paraaortic, and inguinal areas.

The microscopic examination of the lymph node from the inguinal area showed diffuse proliferation of small to medium-sized lymphoid cells with irregular nuclear contour, and admixed lymphoid cells with dispersed chromatin resembling lymphoblasts. The immunohistochemical staining revealed positive expression of cyclin-D1, bcl-2, CD5 (weak), CD20, CD79a and KI-67, and negative expression of CD10, CD23 and CD3 (Fig. 2).

The cellularity of the bone marrow was from 50 to 60%. Bone marrow aspiration revealed blast cells comprising about 77.4% of all hematopoietic nucleated cells. Those cells were mixed small to medium in size with dispersed chromatin, bilobed nucleus, high nucleus/cytoplasm ratio and prominent nucleoli. The staining for myeloperoxidase, PAS, and non-specific esterase was negative. The staining for iron revealed decreased to normal storage iron in marrow particles (Grade

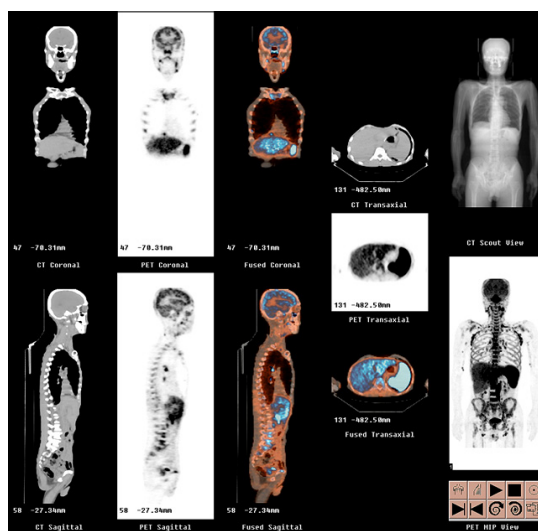


Fig. 1. The increased FDG uptake in the axial skeleton of whole body is noted. The multifocal increase of FDG uptake in multiple lymph node areas including jugular, paratracheal, internal mammary, subcarinal, hilar, anterior and middle diaphragmatic, portocaval, paraaortic, iliac, inguinal, and mesenteric lymph node areas is noted. The increase of FDG uptake in the liver and spleen is also seen.

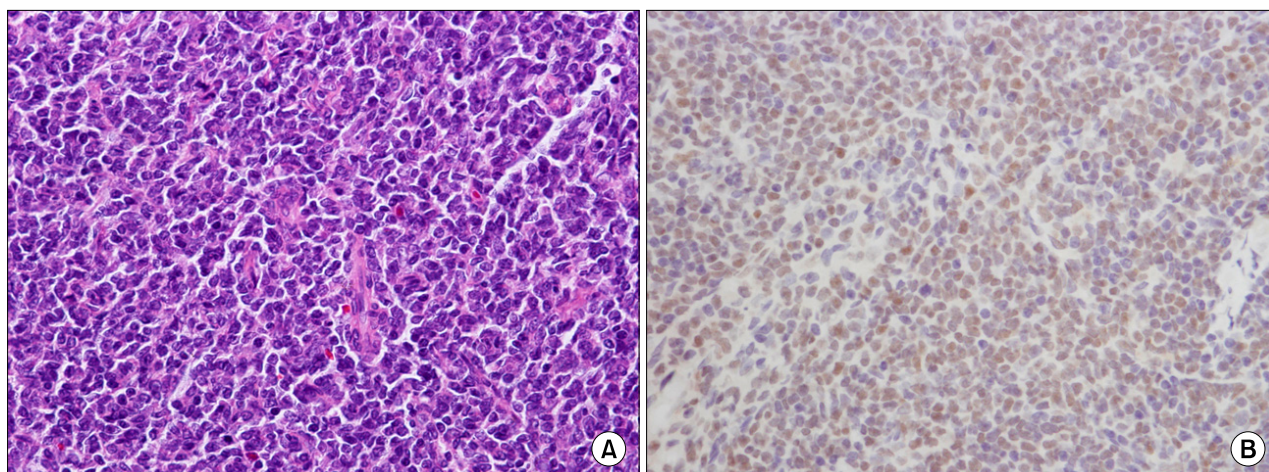


Fig. 2. The microscopic examination of the lymph node from the inguinal area shows diffuse proliferation of small to medium-sized lymphoid cells with irregular nuclear contour, and admixed lymphoid cells with dispersed chromatin resembling lymphoblasts (H-E stain, $\times 200$) (A). The immunohistochemical staining for cyclin-D1 reveals positive result ($\times 400$) (B).

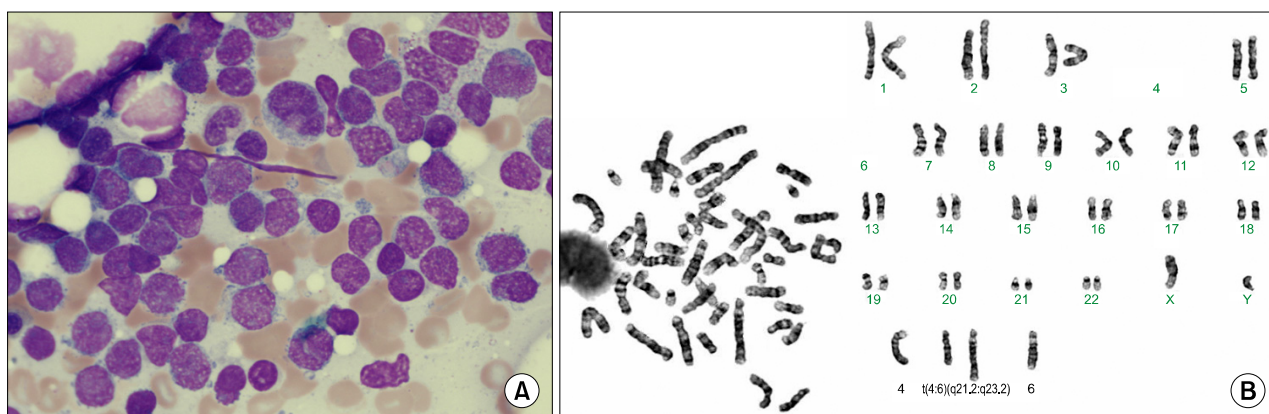


Fig. 3. (A) The Bone marrow aspiration shows many blast cells of small to medium size with dispersed chromatin, high nucleus/cytoplasmic ratio and prominent nucleoli (Wright stain, $\times 1,000$). (B) Cytogenetic study shows chromosomal abnormality of 46,XY, t(4;6)(q21.2;q23.2)[3]/46,XY[37].

I/III). The immunophenotyping study by flow cytometry revealed positive expression of CD20, CD19, FMC7, CD5, CD45, and Sm kappa, and negative expression of CD13, CD33, and myeloperoxidase. The cytogenetic study revealed 46,XY,t(4;6)(q21.2;q23.2)[3]/46,XY[37] (Fig. 3).

Finally, the diagnosis of MCL of the blastic variant with a leukemic presentation which is composed of mixed small and medium-sized cells was made. The lymphoma was considered as a metachronous second primary malignancy, and the onset was 6 years after subtotal gastrectomy for EGC. Considering poor prognostic factors for

MCL including poor performance status, old age, splenomegaly, advanced stage, high LDH, positive cyclin-D1, high serum $\beta 2$ -microglobulin and poor natural course of the MCL with a leukemic presentation, palliative chemotherapy of cyclophosphamide, vincristine and prednisone (CVP) was started in August 2006. Unfortunately the disease was refractory to the first course of CVP, and further chemotherapy was stopped, and after that, only supportive care including hydroxyurea, blood transfusion, nutritional care and antibiotics was given. He died in September 2006.

DISCUSSION

Development of second primary cancers has become an important problem in cancer treatment. The incidence of second primary cancer following gastric cancer had been reported less than 3.4% in Korea^{1,2)}, which is comparable to the report from Japan.³⁾ Significantly elevated risks were observed for cancers of the colorectum, lung and liver.^{1,2)} Meanwhile, the NHL comprised less than 6.3%, and this suggests that the incidence of second primary NHL is very rare.¹⁻³⁾

About 25~40% of the second primary NHL cases were considered to be metachronous, defined as those occurring more than 6 months after the diagnosis of first primary malignancy, and they comprised about 3.6~5.9% of the total of metachronous cancers following gastric cancers.^{1,2)} While Ryu et al. reported 28 month interval between development of gastric cancer and NHL,²⁾ in a report of two cases of lymphoma after Tx of gastric cancer by Nakamura et al, the interval was 7 years in immunoblastic lymphoma subtype and 13 months in MALToma subtype.⁴⁾

Metachronous occurrence of lymphoma and adenocarcinoma, both in the stomach, has been reported. Hamaloglu et al. reported that initial malignancy was NHL in 28 of 30 cases (93.3%), and only 2 cases were diagnosed as NHL after the treatment of adenocarcinoma.⁴⁾ This trend was supported by many authors.^{5,6)} Chemotherapy, radiotherapy, or combined administration of chemotherapy and radiotherapy can increase the occurrence of second malignancies. Gastroesophageal reflux, formation of nitrosamine, and untreated *H. pylori* infection may play a role in development of secondary cancer after gastric surgery.⁴⁾

MCL is a B-cell malignancy with distinct molecular genetics and pathologic features. MCL represents 5~10% of all lymphoma cases in western series, but it comprises about 2% of lymphomas in Korea and Japan.⁷⁾ MCL is a neoplasm

composed of cells resembling those residing in follicular mantle zones. The mantle cells have a distinctive immunophenotype, with expression of pan B-cell markers (CD19, CD20, and CD22) and the T-cell marker CD5; these cells do not express CD23 and CD10 antigens.⁷⁾ Rendering a diagnosis of MCL has been greatly facilitated by the immunohistochemical demonstration of cyclin-D1, because this marker is expressed rarely by other lymphoma types.⁸⁾

MCL of the blastic variant is characterized by monomorphic sheets of small to medium-sized blasts with fine dispersed chromatin mimicking lymphoblastic lymphoma/acute lymphoblastic leukemia. It has narrow rim of cytoplasm and frequent apoptotic bodies. The blastic variant was encountered in 7.2~17% of cases.⁹⁾ In a report, patients with blastic variants presented with more mitoses/HPF, higher LDH levels, and less frequent bone marrow involvement than those with other histologic variants.¹⁰⁾ In another report by Bernard, 66% had extranodal site involvement, 85% had an Ann Arbor stage IV, and 82% had peripheral lymphadenopathy.⁹⁾ In terms of prognosis, the blastic variant was characterized by a shorter overall duration of response after first-line therapy and shorter overall survival.¹¹⁾

In our case, blast cells were found in the bone marrow and circulation constituting a leukemic presentation. The MCL presenting with leukemia appears to be more aggressive and, in several reports, the prognosis was poorer than that of localization to lymph node or extranodal sites.^{8-10,12,13)} The clinical and laboratory variables shown to be of prognostic significance in unselected MCL cases may not appear to have such an impact in those cases presenting with overt leukemia.¹³⁾ In this case, we made a decision to start palliative chemotherapy of CVP considering poor performance status, old age and advanced stage. If the patient is elderly and is not a stem cell transplant candidate, the use of rituximab-containing chemotherapy can be appropriate. Purine nucleoside analogs with rituximab may be especially useful

in the elderly patient population or those who can not tolerate anthracyclines.¹⁴⁾ In patients with relapsed or refractory MCL, the proteasome inhibitor bortezomib may be useful. Even with the most aggressive approaches, a minority of patients with relapsed MCL are cured.

According to the literature, only 40~50% of the patients of MCL exhibited the hallmark t(11;14)(q13;q32), and various chromosomal abnormalities have been reported as well. These include abnormalities involving chromosome 1, 7q, 12, and 10p.¹³⁾ In our case, cytogenetic study revealed 46,XY,t(4;6)(q21.2;q23.2)[3]/46,XY[37] even though the cyclin D1 was overexpressed. In a report by Nam et al, no one showed t(11;14) in G-banding analysis in 12 cases of MCL with marrow infiltration that were diagnosed for over 5 years in a center.¹⁵⁾ The possible reason for the absence of t(11;14) in spite of the expression of cyclin-D1 includes submicroscopic changes involving t(11;14).⁸⁾ Alternatively, t(11;14)-negative MCL can be a new disease entity.¹⁵⁾ The chromosomal abnormality of t(4;6) in this case is an unusual finding and, to the best of our knowledge, there has been no report of such kind of chromosomal abnormality in MCL.

This case is of interest for three reasons. First, metachronous second primary MCL with leukemic presentation following curative resection of EGC is very rare and, to the best of our knowledge, this is the first report of that occasion. Second, MCL was accompanied by unusual cytogenetic abnormality of t(4;6), to the best of our knowledge, that has not been reported yet. Third, the clinician must be astute and aggressive when evaluating a patient with is a history of gastric cancer. Clinical diagnosis of relapsed gastric cancer without pathologic confirmation should be avoided when evaluating patients with lymphadenopathy and abnormal bone uptake.

경과된 시점에서 발생한 속발성 비호지킨림프종 한 예를 보고한다. 림프종 아형 분석 결과 외투세포림프종의 모세포 변이로 밝혀졌고, 백혈병 발현을 보였다. 모세포들은 작거나 중간 크기의 세포로 이루어져 있었다. Cyclin-D1에 대한 면역조직화학염색검사는 양성이었지만, 세포유전학검사에서는 t(4;6) 염색체 이상이 보였다. 국내 보고에서 위암환자에서 속발성 종양의 발생률은 3.4% 미만인데, 림프종은 속발성 종양 중 6.3% 미만을 차지한다. 또한 국내 보고에서 외투세포림프종은 전체 림프종의 2% 미만이고, 모세포 변이의 발현은 흔하지 않다. 저자들이 알기로는 조기위암의 절제술 후 이시성 (metachronous) 외투세포림프종의 백혈병 발현을 보고한 예는 없다. 따라서 본 보고는 이에 대한 첫 증례 보고로 판단된다.

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요 약

저자들은 조기위암에 대한 대부분위절제술 후 6년이

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