Chronic myeloid leukemia associated with signet-ringed adenocarcinoma of stomach and review of the literature

Kronik miyeloid lösemi ve mide adenokarsinomu birlikteliği ve literatür incelemesi

Gönenç Kocabay[1], Betül Tiryaki[2], Kamil Yazıcı[1], Mustafa Yenerel[3]

[1]*Department of Internal Medicine, Istanbul University, Istanbul School of Medicine, Istanbul, Turkey*

[2]*Department of Radiology, Istanbul University, Istanbul School of Medicine, Istanbul, Turkey*

[3]*Departments of Internal Medicine and Hematology, Istanbul University, Istanbul School of Medicine, Istanbul, Turkey*

Chronic myeloid leukemia (CML) is a myeloproliferative disease that is characterized by the proliferation of myeloid cells and their ability to preserve differentiation. Adenocarcinoma of the stomach is a tumor type commonly seen within the fifth and seventh decades. Secondary solid organ malignancies may develop during chronic leukemias. Although this association is commonly seen in chronic lymphocytic leukemia, a secondary tumor may also develop during CML [1, 2]. Chronic myeloid cell leukemia associated with signet-ring type adenocarcinoma of the stomach is rarely seen. Seventeen cases of CML associated with signet-ring adenocarcinoma of the stomach were previously reported in the literature (8 cases in Japan and 9 cases in Europe and the USA) [3, 4].

We report a case of CML associated with signet ring adenocarcinoma of the stomach. We emphasize that a malignancy might develop during CML, especially in the gastrointestinal system, with non-specific symptoms such as weight loss and nausea.

A 47-year-old male patient with no complaints in his history was admitted to our hospital with the complaints of malaise and perspiration. He did not have any specific finding in his medical history. His medical examination did not show any pathological finding except conjunctival pallor. Laboratory findings were as follows: erythrocyte sedimentation rate 90 mm/hour, hemoglobin 9.2 g/dl, hematocrit 26%, MCV 90 fl, leukocyte $170x10^9$/L (neutrophil 80%) and thrombocyte $310x10^9$/L. Six percent blast cells were counted on blood smear, so bone marrow biopsy and aspiration were performed. Differential cell count showed 8% blast cells, 2% eosinophils, 12% basophils, and included hypercellular bone marrow and slightly increased reticulin fibrils, and granulocytic hyperplasia with predominantly increased young cells. Biochemical findings were found normal except for the increased LDH finding. BCR-ABL fusion gene, which was determined by reverse transcriptase polymerase chain reaction (RT-PCR) method, was found positive. Philadelphia chromosome was found as 85% in bone marrow sample. He was diagnosed as CML and hydroxyurea 2 g/day and interferon α 2b (6 million units) were started. All drugs were stopped because of development of thrombocytopenia during interferon therapy, and imatinib mesylate was started as 400 mg/day. He obtained hematologic remission in the 3rd month of this therapy and Philadelphia chromosome was found negative in bone marrow biopsy. BCR-ABL fusion gene could not be found in the 6th month of therapy by the RT-PCR method. He has maintained hematological and cytogenetic remission for three years with imatinib mesylate therapy.

He had complaints of nausea and vomiting, early loss of appetite during meals and weight loss of 5 kg within the next six months. His laboratory findings were as follows: erythrocyte sedimentation rate 24 mm/hour, CRP 85 mg/l, hemoglobin 14 g/dl, hematocrit 42%, leukocyte $12x10^9$/L (neutrophils $8.8x10^9$/L) and thrombocyte $400x10^9$/L; biochemical findings

Address for Correspondence: Dr. Gönenç Kocabay, Department of Internal Medicine, Istanbul University, Istanbul School of Medicine, Istanbul, Turkey
Phone: +90 216 451 87 87 E-mail: gonenckocabay@yahoo.com

were normal. Endoscopic examination was planned to investigate clinical and laboratory findings. Upper gastrointestinal endoscopy revealed a patchy ulcerated and erose solid tumor almost obstructing the lumen on the proximal antrum. A biopsy was taken and the pathological examination showed a slightly differentiated adenocarcinoma that produced mucin and included signet ring cell. Lymph node and liver metastasis were not found by imaging methods and he was referred to the Department of General Surgery.

Niitsu and colleagues [1] reported that stomach, breast and esophageal cancers were commonly seen (in 8.3% out of 674 patients) in patients with a hematological malignancy. A secondary solid organ malignancy may develop during hematological malignancy such as CML. Any patient with cancer usually has increased risk of development of a secondary cancer [5]. Moertel and colleagues [2] found 11 cases (2.1%) of malignancy-associated malignancy in 528 cases of CML in a 10-year period in the Mayo Clinic. They showed that leukemia increased the cancer occurrence rate. Another study conducted recently on this issue in Johns Hopkins Hospital revealed 14 cases (14%) of associated cancer in 90 CML patients in a 10-year period and the majority of patients were older than 30 years. Their report included only one case of stomach adenocarcinoma. Carruth and colleagues [3] reported an 18-year-old male who had Philadelphia chromosome-positive CML associated with stomach adenocarcinoma.

Fujii [6] reported a 46-year-old female with Philadelphia chromosome-positive CML associated with stomach adenocarcinoma and five cases of CML with stomach adenocarcinoma in Japan. In later years at least three other case reports were presented in the Japanese literature [7-9].

The finding of positive Philadelphia chromosome is remarkable in this presented case and other case reports. The presence of Philadelphia chromosome excludes the hypothesis that CML is a paraneoplastic finding of stomach adeno cancer. Pathogenesis of gastrointestinal malignancies might be attributed to the drugs used in CML therapy or the immune system dysfunction caused by leukemia [10].

Our patient was treated with hydroxyurea and interferon α-2b. Imatinib mesylate was started after a short time because of the development of thrombocytopenia during interferon therapy. He had used this therapy for three years. Although there are some recent studies about imatinib mesylate with genitourinary tumors in rats [11,12], preliminary analysis of the safety data from clinical trials and adverse event reports do not support these findings. While association of two different malignancies usually does not negatively affect prognosis, each malignancy should be treated specifically [10].

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