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SHORT COMMUNICATIONS AND CASE REPORTS

The development of metachronous prostate cancer and chronic myeloid leukemia in a patient with metastatic rectal cancer

I. Oztop[1], A. Yaren[2], M. Demirpence[1], I. Alacacioglu[1], B. Tuna[3], O. Piskin[1], U. Yilmaz[1]

[1]Dokuz Eylul University, Institute of Oncology, Izmir; [2]Pamukkale University, Faculty of Medicine, Department of Internal Medicine, Division of Medical Oncology, Denizli; [3]Dokuz Eylul University, Faculty of Medicine, Department of Pathology, Izmir, Turkey

Summary

We report herein an unusual case of metachronous triple cancers (rectum, prostate and Philadelphia$^+$ [Ph$^+$] chronic myeloid leukemia [CML]). A metastatic rectal cancer was diagnosed in a 76-year-old male patient, who was treated with transanal tumor resection and chemotherapy. Thirty months from the initial rectal cancer diagnosis, prostate cancer was diagnosed and the patient was administered maximal androgen blockade and received palliative radiotherapy to the lumbar spine because of painful bone metastases. Thirty months after the diagnosis of rectal cancer and 12 months after the diagnosis of prostate cancer the patient developed Ph$^+$ CML and imatinib treatment was started. After one-year period in remission, CML evolved into accelerated phase and the patient died of intracranial hemorrhage.

Key words: chronic myeloid leukemia, metachronous, multiple cancers, prostate cancer, rectal cancer

Introduction

Related to the recent improvements in the diagnosis of malignant tumors, long life span and increase of the cancer incidence, a rise has been witnessed in the number of patients with multiple cancers. Nevertheless, triple cancers are rare and most of them are seen as part of hereditary cancer syndromes or develop due to the field cancerization theory (such as head-neck, lung and esophagus cancers) [1,2]. Multiple cancers can also develop as synchronous or metachronous. Generally, cancers developing within one year are accepted as synchronous while those developing more than one year are characterized metachronous cancers [3]. Some of the metachronous cancers may develop owing to the treatment of the primary disease (radiation-induced cancers, chemotherapy-induced leukemias, etc.) [4].

While prostate cancer is the most common type of cancer in men, colorectal cancer takes its place as the third most common. The incidence of cancer increases with age and about 60% of malignant diseases occur in persons over 65 years [5]. In other words, the risk of cancer development is 11-fold higher in the population over 65 as compared with younger groups [6]. As a result, with the increase of age, an increase in the development of multiple cancers in elderly populations is to be expected.

While assessing symptoms and findings of a given primary cancer it would be prudent to bear in mind that the clinical and even the laboratory picture could be due to a second cancer, especially in older persons. Attributing symptoms and signs directly to the primary disease may not only cause delay of true diagnosis, but also may lead to an insufficient or erroneous treatment. In this manner, the present case was firstly diagnosed as metastatic rectal cancer and then developed metachronous prostate cancer and bears the uniqueness of the development of CML, i.e. two important malignancies (prostate cancer and CML) which should be taken into consideration in terms of distinctive diagnosis in older patients as a reason of increase of the leukocyte count and bone metastasis that may appear during the follow up period of the primary disease.

Correspondence to: Ilhan Oztop, MD. 173/5 sokak, No: 6, Daire:7, Basinsitesi, Izmir, Turkey. Tel: +90 232 412 48 02, Fax: +90 232 278 94 95, E-mail: ilhan.oztop@deu.edu.tr

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Case presentation

A 76-year-old male patient was admitted to the general surgical department of our hospital complaining of gastric pain and rectal bleeding. On physical examination hepatomegaly (3 cm below the arcus costarium) and tenderness on the right upper quadrant of the abdomen were found. Chest radiography and abdominal computerized tomography (CT) revealed multiple liver and pulmonary metastases, as well as prostate hypertrophy. Colonoscopy showed a polypoid mass in the lumen of the proximal rectum which was biopsied and the histopathological examination showed adenocarcinoma. The patient's complete blood count and serum biochemistry were within normal limits during this period. His serum carcinoembryonic antigen (CEA) and prostate specific antigen (PSA) levels were within normal limits. Transanal rectal resection was carried out and the pathologic examination of the surgical material showed adenocarcinoma (locoregional stage pT4N1; Figure 1). The patient was staged as T4N1M1 because of the liver and pulmonary metastases, and received combination chemotherapy with infusional 5-fluorouracil/leucovorin (5-FU/LV)+irinotecan (CPT-11) (FOLFIRI). CT evaluations made after the 6th and 12th cycle showed stable disease and treatment continued to 18 cycles. Serum CEA levels were normal during this period. After the 18th cycle the disease progressed in the lungs, however liver metastases were stable and serum CEA was also normal during this period (3.54 ng/ml, normal range 0-4). The treatment was stopped and the patient was followed every 3 months without treatment.

After 13 months from stopping chemotherapy and 30 months from the diagnosis of rectal cancer, chest and abdominal CT as well as bone scintigraphy were carried out because of prostatic symptoms and backache. Lung and liver metastases were stable, while the prostatic volume was increased and osteoblastic metastases in the lumbar vertebrae were detected on CT and multiple bone metastases were seen in bone scintigraphy. Serum PSA was 750 ng/ml (normal range 0-4). Prostate biopsy showed adenocarcinoma with Gleason score 8 (Figure 2). The diagnosis was confirmed after positive immunohistochemical staining with prostate-specific acid phosphatase (PSAP) (Figure 3) and negative high-molecular weight kininogen (HMWK). The patient was put under maximal androgen blockage (MAB) treatment with the LH-RH analogue goserelin and antiandrogen treatment with bicalutamide. In addition, radiotherapy was delivered to the lumbar spine. Gradually prostatic symptoms and backache subsided and serum PSA value returned to normal. Also, repeat chest and abdominal CT showed stable disease in the lungs and liver; there was also a mild increase in CEA level (4.17 ng/ml), not very different from the one taken 3 months ago.

On the 12th month of his MAB treatment, the patient, who had interrupted his follow up for 6 months, reapplied to our clinic complaining of asthenia and weight loss. On physical examination hepatosplenomegaly was detected and full blood count was as follows: white blood cells (WBC) 274×10^9/L, Hb 10.6 g/dl, and platelet count 114×10^9/L. Peripheral blood examination showed great number of immature cells of the myeloid and erythroid lineage. Leukocyte alkaline phosphatase (LAP) was decreased. Bone marrow aspiration showed hypercellular bone marrow and the proportion of myeloid/erythroid lineage was 19/1, consistent with CML (Figure 4). Hydroxyurea 1000 mg/day was started until the result of the cytogenetic analysis which showed Ph^+ CML with 83% FISH:BCR-Abl

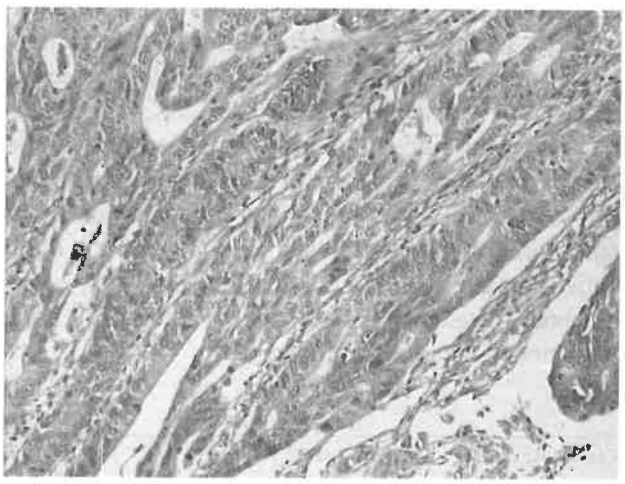


Figure 1. Rectal adenocarcinoma (H&E ×10).

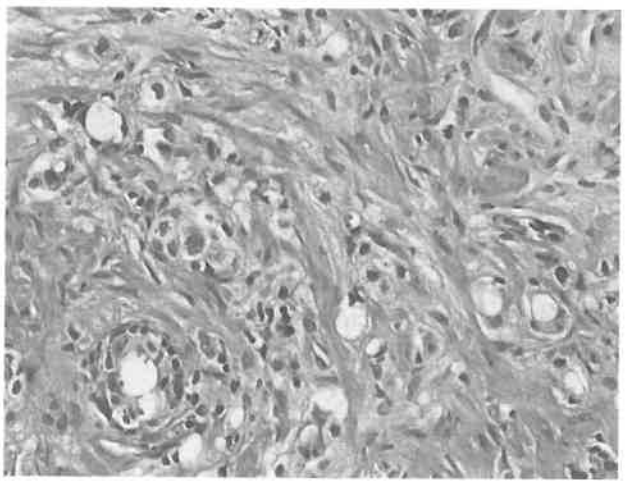


Figure 2. Prostate adenocarcinoma (H&E ×10).

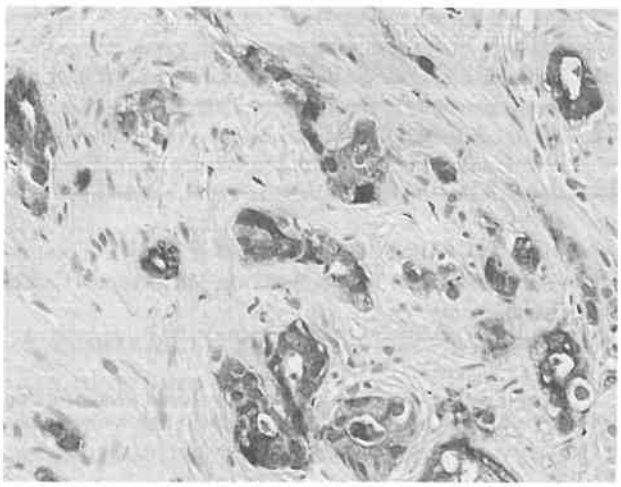


Figure 3. PSAP reactivity in prostatic adenocarcinoma cells (×10).

positivity; imatinib mesylate (gliveç) 400 mg/day was added to the treatment. After 2 months the patient's clinical condition showed a clear improvement. Clinically hepatosplenomegaly disappeared and the WBC dropped to 9.6×10^9/L. Hydroxyurea was stopped and treatment continued with glivec 400 mg/day. After a while grade 3 thrombocytopenia was observed and the dose of glivec was decreased to 200 mg/day for the following 6 months. At the end of this period an increase in WBC was detected, and peripheral blood smear examination and bone marrow aspiration showed accelerated phase of CML. The patient declined further treatment. During this period rectal and prostate cancer were stable. After 48 months from the diagnosis of rectal cancer, 18 months from the metastatic prostate cancer, and 8 months from CML diagnosis, the patient died of intracranial hemorrhage, most probably due to intracranial bleeding from accelerated phase of CML.

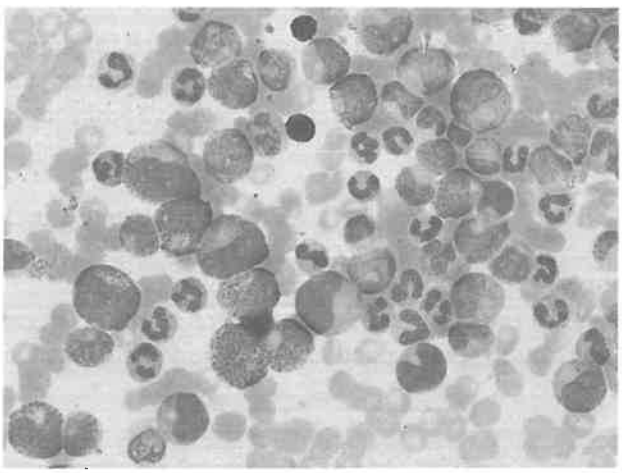


Figure 4. Increased cellularity due to left shifted granulopoiesis in the chronic phase CML (Wright ×100).

Discussion

Multiple cancers in the same patient are relatively more frequently diagnosed due to the population's greater life expectancy and improvements in the diagnostic methods. A wide variety of second cancers have been described with latency periods of 10 years for solid tumors and 5 years for leukemia. Aggressive cancer treatment approaches have improved curability; however, prolonged administration of chemotherapy, especially alkylating agents, and the use of radiotherapy have been major risk factors in the development of second cancers [7].

Although there is general agreement about the diagnosis of multiple cancers in the literature, no exact criterion exists to characterize synchronous and metachronous neoplasms. Different cancers have different growth rates, however some authors suggest that cancers developing within one year are generally synchronous and those developing in more than one year are metachronous [3,8]. In this concept, the malignancies of our case should be characterized as metachronous cancers because of their development periods.

Most of the multiple cancers mentioned in the literature develop as part of hereditary cancer syndromes or due to the field cancerization theory [1,2]. Head & neck cancer, lung cancer and esophageal cancer, which are -at least in part- the result of exposure to alcohol and cigarette smoking, can be observed as synchronous or metachronous, as well as double or triple cancers. With increasing age, rectal, prostate and renal cancers are a metachronous event [9], prostate cancer and CML a synchronous event [10], and in a case CML developed as a metachronous event following colon cancer [11]. In the literature only a limited number of cases with multiple metachronous cancers can be found, especially with triple metachronous cancers. The case we presented herein is also quite important in terms of distinctive diagnosis. Because the incidence of cancer is increasing with age and among cancers developing in relation to the increase of age, colorectal cancers and CML, as well as prostate cancer have important roles. If the symptoms of one of the cancers prevail, this may not only cause delay of the true diagnosis, but also may lead to an insufficient or erroneous treatment. In our case sclerotic bone metastases were found after 30 months from the first rectal cancer diagnosis. These lesions were not directly accepted as bone metastases of rectal cancer, but with a broader diagnostic workup which showed increase of the prostate volume in abdominal CT, prostate cancer was taken into consideration and proven by biopsy. As a result not only radiotherapy to the spine was delivered but also a to-

tally different therapeutic approach (hormonotherapy) was used to manage the patient's symptoms. After a year from the prostate cancer diagnosis, a gradually increasing leukocytosis was thought to be related to leukemoid reaction or bone marrow involvement. In patients with solid tumors, endogenous production of various cytokines such as granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage-CSF, interleukin-1 and interleukin-6, can lead to leukemoid reaction [12,13]. However, with the low score of LAP, we excluded the leukemoid reaction and no solid tumor involvement in bone marrow biopsy was seen. Bone marrow aspiration and cytogenetic examination revealed Ph^+ CML, so that a totally different treatment (imatinib) from the previous solid tumors treatments was administered to the patient.

In conclusion, since cancer incidence is positively related with increasing age, it should be kept in mind that the possibility always exists to come across multiple cancers, especially in older patients, before attributing new data to a known primary cancer.

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