Case Report

Hepatocellular Carcinoma and Bladder Cancer as Complications Following Five Years of Chemotherapy for Acute Myeloblastic Leukemia

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Acute myeloblastic leukemia (AML) was diagnosed in a 54-year-old male, a chronic hepatitis B surface antigen (HBsAg) carrier, in June, 1983. Prompt remission was achieved, and maintenance and intensification chemotherapy were given for five years. He was readmitted in March, 1988 because of a mass in the liver and was diagnosed as having hepatocellular carcinoma (HCC). Curative right segmentectomy was performed in May, 1988. In December, 1988, transitional cell carcinoma of the bladder was discovered, and resected transurethrally. These secondary neoplasms, HCC and bladder cancer, were thought to be associated with the long-term chemotherapy given for the AML.

Key words: Acute myeloblastic leukemia, Secondary cancer

Cases of multiple primary cancer associated with hematological malignancy have increased with recent advances in diagnostic techniques and cancer chemotherapy (1). We report here a case of hepatocellular carcinoma (HCC) and bladder cancer occurring as complications following five years of chemotherapy for acute myeloblastic leukemia (AML).

CASE REPORT

A 54-year-old man was first admitted to our hospital in June, 1983 because of fever and petechiae. He had smoked 20 cigarettes daily between 1965 and 1980 but had no other risk factors for bladder cancer, including chemical exposure or environmental factors. His mother and brother were hepatitis B surface antigen (HBsAg)-positive. On admission, hematological values were as follows: hemoglobin, 7.2 g/dl; white blood cell count (WBC), 7,800/mm$^3$ with 85% myeloblasts; platelet count, 0.9 x 10$^4$/mm$^3$. Liver function tests disclosed the following values: total bilirubin, 0.4 mg/dl; SGOT, 14 IU/l; SGPT, 13 IU/l; $\gamma$-GTP, 51 IU/l; HBsAg, positive; HBe antibody, negative. The bone marrow showed 68.0 x 10$^4$ nucleated cells/mm$^3$ with 98% myeloblasts (Fig. 1). After diagnosis of acute myeloblastic leukemia (AML, FAB: M1), the patient was treated with one course of combination chemotherapy consisting of behenolyl-Ara-C (BHAC), daunorubicin (DM), 6-mercaptopurine (6-MP) and prednisolone (BHAC-DMP), which induced a complete remission. During the pancytopenic period following this first course of chemotherapy, the patient suffered from septicemia caused by Bacillus cereus and liver abscess caused by Streptococcus faecalis. His condition improved after treatment with antibiotics and liver drainage. After three courses of BHAC-DMP combination chemotherapy, the patient was discharged in October 1983. Maintenance and intensification chemotherapy were
administered at 3-month intervals for five years (total dosages: cyclophosphamide (EDX), 8,400 mg; 6-MP, 16,900 mg; vincristine, 24 mg; DM, 1,100 mg; BHAC, 7,700 mg). The patient was readmitted in March, 1988 because of a mass detected in the right lobe of the liver by ultrasonography. Physical examination revealed no enlargement of the liver or spleen. Cardiac, pulmonary and neurologic functions were normal. During the second admission, urinalysis showed transient hematuria, but hematological values were all within normal limits. Laboratory studies disclosed the following values: serum total protein, 7.7 mg/dl (65.0% albumin); total bilirubin, 0.7 mg/dl; SGOT, 41 IU/l; SGPT, 34 IU/l; alkaline phosphatase, 335 IU/l (normal 60–250); γ-GTP, 140 IU/l; ICG retention, 7.7% in 15 minutes; serum alpha fetoprotein (AFP), 180.1 ng/ml; HBsAg and hepatitis B core antibody (HbcAb), positive; HBe antigen, negative. No evidence of liver cirrhosis was found. Celiac angiography showed a huge solitary tumor in the right lobe of the liver (Fig. 2). He was diagnosed...
as having HCC and curative right segmentectomy was performed in May, 1988 after transcatheter arterial embolization. The gross specimen weighed 2,100 g and contained a single, well circumscribed HCC measuring 17.1 x 12.7 cm (Fig. 3) of Edmonson II type associated with chronic hepatitis. After surgical resection of the hepatic tumor, the AFP level decreased to 10.7 ng/ml and HBsAg and hepatitis B virus associated-DNA polymerase (HBV-DNA-P) became undetectable in the serum within one month.

In December, 1988, the patient suffered macrohematuria and was admitted to the Department of Urology. Transurethral resection of a grade II papillary transitional cell carcinoma of the bladder (Fig. 4) was performed in December, HBsAg and HBV-DNA-P have been negative for 1 year and the patient has been doing well since January, 1989.

**DISCUSSION**

Epidemiologic evidence suggests an etiologic relation between hepatitis B virus (HBV) infection and primary HCC (2). Integration of HBV-DNA in liver tissue has been found in 80–90% of patients with HCC showing positive HBsAg (3–5). After resection of the tumors from the present patient, HBsAg and HBV-DNA-P became undetectable in the serum within 1 month and at the time of writing have not been detected for more than one year. Among 64 patients with HCC followed up for more than 6 months after resection, 4 subsequently became negative for serum HBsAg (6). Two patients who had shown tissue HBsAg exclusively in the tumor quickly became negative for HBsAg after resection. The other 2 patients showed delayed HBsAg clearance. One had tissue HBsAg in both the tumor and non-tumorous liver tissue. Only 1 patient had tissue HBsAg in the liver, but not in the tumor.

The HBsAg clearance observed after resection in our patient confirmed that HBsAg was present exclusively in the tumor cells. Thus it was suggested that HBV could have been one factor contributing to the development of HCC in the present case.

Multiple primary cancer associated with hematological malignancies has been noted along
with recent advances in diagnostic techniques and cancer chemotherapy. According to a questionnaire survey of multiple primary cancers associated with hematological malignancies in adults, there have been four cases of hepatoma subsequent to hematological malignancies in Japan (1). These hematological malignancies included two multiple myelomas, one Hodgkin’s lymphoma and one polycythemia vera. Recently, a case of hepatocellular carcinoma in a long-term survivor of acute lymphocytic leukemia was reported (7). However, we were unable to find any reports of hepatoma subsequent to AML in adults. This would appear to indicate that AML as an initial cancer preceding hepatoma is very rare. In our present patient, as hepatoma had developed in a setting of chronic hepatitis, we think that an additional factor besides HBV, for example immunosuppression or suppression of the anti-tumor immune defense mechanism due to chemotherapy, may have played an important role in the course of HCC development.

Furthermore, the patient also developed bladder cancer. Although the patient had received long-term multidrug chemotherapy including EDX, it is difficult to establish a causal link between the anticancer drugs and the bladder cancer. Among the drugs that the patient received, EDX is the only one that has been shown to be a human carcinogen (8, 9). There is abundant literature about bladder cancer following administration of this agent (10–16). Therefore we speculate that the bladder mucosa was damaged and humoral and cell-mediated immune defense was suppressed by EDX, and that the other combined drugs promoted the transformation to cancer. Although patients with bladder cancer following EDX therapy have been reported to experience hemorrhagic cystitis during therapy (11, 14), this did not occur in our patient. Bjergaard et al reported that no increased risk of bladder carcinoma was seen in a large cohort study of 471 patients in whom hemorrhagic cystitis developed (16). Tobacco-smoking and exposure to compounds such as aromatic amines are known to induce carcinoma of the urinary bladder (17, 18). Such factors, especially smoking, may not have been contributory in the present case, because the patient had stopped smoking five years previously. There is a 9-fold higher incidence of bladder cancer in patients receiving EDX in comparison with non-EDX-treated cancer patients, and a 45-fold higher incidence in comparison with the general population (12). All case reports of EDX-associated bladder cancer have involved patients on long-term EDX treatment and in whom the bladder cancer was noted between 9 months and 10.5 years after termination of the therapy. A total dose of 25–300 g of EDX appears to be the most important risk factor associated with the development of bladder cancer (16, 19). As to the total dose of EDX in our patient, when EDX is used in combination therapy rather than as a single agent, it may become difficult to separate the future long-term toxicity of such combinations from the individual toxicities of each drug. Thus, intermittent dosage schedules including EDX dosage rate as high as that in our patient may induce cancer cells with a higher degree of malignancy compared with a daily continuous oral dosage.

It is difficult to calculate reliably the incidence of secondary malignancies due to antineoplastic agents because very few studies have given details regarding total numbers of patients in the groups in which a second malignancy has occurred. The secondary neoplasms, hepatoma and bladder cancer, observed in the present patient might have been attributable to the long-term chemotherapy given for the AML. This case clearly indicates the need for a careful systematic follow-up of long-term survivors of AML.

REFERENCES

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Secondary Cancer in a Case of AML