Quadruple Cancers in a Human T-Cell Leukemia Virus Type 1 Carrier

Tatsuyuki MORI, Kazunori NAKASE, Kota TSUJI, Syozaburo NAGAYA, Takeshi IKEDA,
Motoaki TANIGAWA, Shigehisa TAMAKI, Eiki MIYANISHI, Kenkichi KITA* and Shigeru SHIRAKAWA*

Human T-cell leukemia virus type 1 (HTLV-1) infection is considered to contribute to the risk of malignancies other than adult T-cell leukemia. We report a 64-year-old male HTLV-1 carrier who developed quadruple malignancies such as cancer of the urinary bladder, skin, larynx and liver.

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Key words: HTLV-1 carrier, multiple cancers

Introduction

It is well known that human T-cell leukemia virus type-1 (HTLV-1) is the causative pathogen of adult T-cell leukemia (ATL) (1) and HTLV-1 associated myelopathy (2). HTLV-1 is also thought to alter the host immune function and to contribute to the development of other malignancies (3, 4).

In this report, we present an HTLV-1 carrier who developed quadruple carcinomas. To our knowledge, multiple cancers totaling four or more have not been reported previously in an HTLV-1 carrier.

Case Report

A 64-year-old man was admitted to our hospital because of hoarseness in 1989. He and his parents were born in Osaka Prefecture, Japan and both parents had died of unknown cause. Two of his older sisters had died of colon cancer and renal cancer, respectively. He had been a heavy drinker [360 ml of Japanese rice wine (sake) a day for 35 years] and smoker (15 cigarettes a day for 40 years). There was a history of bladder cancer (Fig. 1A) in 1982, shaped as a pedunculated papillary tumor, approximately 3 cm in size, and was treated with partial cystectomy and anti-cancer agents of a total intravenous dose of 30 mg Mitomycin C, with Doxorubicin 1,350 mg and Cytarabine 13.5 kg given intrablastically. At this time he received blood transfusions (9 units of preserved whole blood, 3 units of red cell concentrates and 21 units of fresh frozen plasma). In addition, he had a total resection of skin cancer (Fig. 1B) of the left auricle, 1.5×1.0 cm in size, in 1987. There was no evidence

of recurrence of either carcinoma.

Laboratory data on the present admission in 1989 were as follows; red blood cell $366 \times 10^4/\mu\text{l}$, hemoglobin 13.5 g/dl, hematocrit 39.1%, white blood cell $3,300/\mu\text{l}$ with normal differentials, platelet $8.4 \times 10^4/\mu\text{l}$, total protein 7.1 g/dl, albumin 3.8 g/dl, total bilirubin 0.7 mg/dl, cholinesterase 0.55 ΔPH , alkaline phosphatase 64 IU/l, glutamate pyruvate transaminase 59 IU/l and glutamate oxaloacetate transaminase 46 IU/l. Immunoglobulin G (IgG) was 1,060 mg/dl, IgA 217 mg/dl and IgM 71 mg/dl. The surface markers of peripheral blood lymphocytes were as follows; CD3 68.7%, CD4 32.1% and CD8 38.5%. Anti-HTLV-1 antibody was positive ($\times 4,096$) by particle agglutination test and determined by Western blotting. Anti-hepatitis C virus (HCV) antibody was also positive in the serum. Vocal cord biopsy revealed squamous cell carcinoma (Fig. 1C) (T2N0M0, TNM classification) and he was treated with irradiation in 1989. Also, an echographic examination of the abdomen disclosed a mass lesion, 2.6×2.6 cm in size, in the liver. He had a partial hepatectomy and was diagnosed as hepatocellular carcinoma (Fig. 1D) with liver cirrhosis in the same year. Neither peripheral lymph node swelling nor abnormal lymphocytes in the peripheral blood smear has been seen during the clinical course. He is alive now and is followed up as an out-patient.

Analysis of HTLV-1

A monoclonal integration of HTLV-1 proviral DNA was negative by Southern blot analysis. But, viral integration was positive by polymerase chain reaction (PCR) analysis (Fig. 2) on the DNA extracted from the mononuclear cells of peripheral

From the Department of Internal Medicine, Yamada Red Cross Hospital, Misono and *the Second Department of Internal Medicine, Faculty of Medicine, Mie University, Tsu

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Reprint requests should be addressed to Dr. Kazunori Nakase, the Department of Internal Medicine, Yamada Red Cross Hospital, Misono, Mie 516

Fig. 1. Histological findings of quadruple carcinomas (HE stain). A) Transitional cell carcinoma of the urinary bladder ($\times 100$). B) Basal cell carcinoma of the skin ($\times 40$). C) Squamous cell carcinoma of the larynx ($\times 40$). D) Hepatocellular carcinoma ($\times 200$).

Fig. 2. Analysis of HTLV-1 proviral DNA by PCR method. M, marker (X174-HaeIII fragments). 1) negative control (Raji cell DNA $1 \mu\text{g}$). 2) positive control (MT-2 cell DNA 1 ng /Raji cell DNA $1 \mu\text{g}$). 3) positive control (MT-2 cell DNA 100 pg /Raji cell DNA $1 \mu\text{g}$). 4) positive control (MT-2 cell DNA 10 pg /Raji cell DNA $1 \mu\text{g}$). 5) patient DNA $1 \mu\text{g}$. 6) patient DNA 500 ng . 7) patient DNA 100 ng . 8) buffer control.

blood. HTLV-1 proviral DNA on fixed hepatocellular carcinoma cells was not detected by PCR analysis. A probe for proviral DNA used was a 8.25 kb fragment of λ 23-3 (Oncor Inc., Gaithersburg, MD). The primer used for PCR was described previously (5).

Discussion

In this report, we describe a case of HTLV-1 carrier who developed quadruple cancers. The patient was positive for anti-HTLV-1 antibody but lacked evidence of overt ATL such as lymph node swelling and abnormal lymphocytes in the peripheral blood smear. So, we diagnosed him as a carrier state of HTLV-1. In this case, two routes of HTLV-1 infection, namely, from mother to child or from donor to recipient in blood transfusion were considered (6, 7). ATL has a peculiar geographic distribution in the southwestern part of Japan (8, 9). However, since the birthplace of the patient and his mother was not that area, the first route of HTLV-1 infection is unlikely. Concerning the possibility of transmission from wife to husband, we could not test his wife's serum due to her refusal. Though this route can not be completely excluded, it is extremely rare (10). We think that the blood transfusion was the more possible infectious route of HTLV-1 because the patient was transfused before the introduction of a screening system for anti-HTLV-1 antibody in Japan. At that time, he might have also been infected with HCV.

Since the 1970's, many investigators have reported a tendency of multiple primary cancers with increasing incidence (11, 12). However, cases with multiple carcinomas totaling four or more are extremely rare (13). A report from Mayo Clinic described only 5 cases (0.0001%) of quadruple or more primary cancers in 37,580 consecutive autopsy cases (14). The occurrence of second malignancies due to anti-cancer drugs, especially alkylating agents, has been reported (15). In the present case, Mitomycin C, Doxorubicin and Citarabin were administered for bladder cancer in 1982. To our knowledge, however, the malignancies induced by chemotherapy such as this regimen have not been documented previously. A high HTLV-1 seroprevalence in patients with malignancy irrespective of blood transfusion has been reported (16). Although this issue is controversial (17), HTLV-1 infection was demonstrated to be directly or indirectly associated with the oncogenesis of a malignancy other than ATL (3, 18). Matsuzaki et al described monoclonal integration of HTLV-1 proviral DNA in small cell lung cancer cells and suggested its direct involvement in carcinogenesis (19). Our analysis of hepatocellular carcinoma cells did not have this finding. HTLV-1 infection is also thought to alter the host immune surveillance system and to permit evolution of various malignancies (4). The present patient did

not show any evidence of immune deficiency as far as we could determine. In this case, however, the development of multiple cancers other than the urinary bladder cancer may have been associated with HTLV-1 infection perhaps by indirect mechanisms though the details are unclear.

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