A Cholangiocellular Carcinoma with an Aggressive Growth and Eosinophilia, which Showed Multiple Myeloma in Autopsy

Key words: cholangiocellular carcinoma, hypereosinophilic syndrome, multiple myeloma

Cases of cholangiocellular carcinoma (CCC) with marked eosinophilia are seldom encountered. We encountered a case of CCC with marked eosinophilia, which showed a very progressive course and also showed multiple myeloma (MM) in autopsy.

A 55-year-old man was admitted to our hospital on November, 1999 because of high fever and epigastralgia since October 1999. He exhibited hepatomegaly palpable at...
2 fingerbreadths below the right costal margin. Laboratory examination was negative for hepatitis B surface antigen (HBsAg), hepatitis C antibody (HCV), human immunodeficiency virus (HIV), and human T-cell leukemia virus type I (HTLV-1). Marked leukocytosis with eosinophilia were shown as a white blood cell count of 26.3x10^3/μl (metamyelocytes 1%, band forms 18%, segmented forms 46%, lymphocytes 10%, monocytes 4%, eosinophils 20%, basophils 1%), a red blood cell count of 434x10^6/μl, a hemoglobin of 13.0 g/dl, and a platelet count of 37.8x10^9/μl. No liver dysfunction and no jaundice were observed, and C-reactive protein level was 5.8 mg/dl. Carcinoembryonic antigen, CA19-9, and alpha-fetoprotein levels were normal. Stool examination was negative for parasitic infection. Serum IgE level was normal and soluble interleukin-2 receptor level was 8,580 U/ml. Serum cytokine levels including granulocyte-macrophage colony-stimulating factor (GM-CSF), transforming growth factor-beta (TGF-β), interleukin-3 (IL-3), interleukin-5 (IL-5), and interleukin-6 (IL-6) were 99.6 pg/ml, 9.16 ng/ml,<31.3 pg/ml, <7.8 (normal ≤10) pg/ml, and 42.4 (normal ≤4.0) pg/ml, respectively. Computed tomography of the abdomen revealed small (1–2 cm in diameter) low-density lesions predominantly in the left lobe of the liver, but no lymphadenopathy was found. Findings of gastrofiberscopy, total colonoscopy, and urological study were normal. Bone marrow aspiration revealed hypercellular marrow with proliferation of eosinophils to 21.6%, and plasma cells to 10.0%, and chromosomal examination revealed 47, XY, +7 (1/20), and 46, XY (19/20). No M-bow was found in the electrophoresis. Antigens of Fasciola hepatica and Toxocara canis were positive on Ouchterlony’s double diffusion test.

After we ruled out echinococcus infection, transcutaneous needle liver biopsy was done and revealed that CCC of the liver was most probable. A series of chemotherapy treatments with carboplatin and fluorouracil via hepatic artery infusion did not improve his disease, and he died of bone marrow suppression and pulmonary bleeding on February 19, 2000. Findings of autopsy revealed CCC (moderately–poorly differentiated tubular adenocarcinoma) (Fig. 1A, B), massively occupied the whole liver. Cancer metastasis was found in the lymph nodes of the peripancreatic and retroperitoneal regions and in the sternum. In addition to these findings, MM (IgL-λ) was found in moderately cellular marrow with osteolytic mass formation (Fig. 1 C, D). Immunochemical staining for GM-CSF on the CCC was negative.

Cases of CCC with marked eosinophilia are seldom encountered, and no such case report can be found, although a small number of hepatocellular carcinomas with eosinophilia have been reported (1). It was very difficult to determine an etiology of eosinophilia in this case at first. Because he had traveled to an area where many wild foxes and dogs exist and habitually ate raw vegetables, we considered a parasitic disease as a differential diagnosis. It was confusing that the antigens of Fasciola hepatica and Toxocara canis yielded a nonspecific reaction just 5 days before the patient died.

Although the serum levels of some cytokines were markedly elevated, immunochemical staining for GM-CSF on the CCC was negative. Although no GM-CSF production from the CCC was observed, recent studies revealed that eosinophilia is induced by cytokines, such as IL-5, IL-3, etc., derived from activated T cells distant from malignant cells (2–4). Serum and tumor tissue extracts stimulated the growth of granulocyte, monocyte, and eosinocyte colonies in semi-solid cultures of human bone marrow, which was inhibited by the addition of antibodies to GM-CSF and IL-3 (5). These findings show a possibility that GM-CSF play a role in the pathogenesis of eosinophilia associated with some malignant tumors. Findings of autopsy mainly revealed poorly differentiated CCC of the liver and MM in bone marrow. No parasitic lesions were found. The frequency of association of MM is not higher than the overall incidence of second malignancies in patients with cancer, and only one report of MM associated with CCC can be found; it is in Spanish (6). For the reasons indicated above, it was very difficult to diagnose and treat this rare so-called “paraneoplastic syndrome”.

Yoshinobu Seki, Koji Sato, Osamu Isokawa* and Gou Hasegawa**

The Department of Internal Medicine, Niigata Prefectural Koide Hospital, Niigata, *the Department of Internal Medicine, Nagaoka Redcross Hospital, Nagaoka and **the Second Department of Pathology, Niigata University Medical Hospital, Niigata

Received for publication January 14, 2003; Accepted for publication August 14, 2003

Reprint requests should be addressed to Dr. Yoshinobu Seki, the Department of Internal Medicine, Niigata Prefectural Shibata Hospital, 4-5-48 Otemachi, Shibata, Niigata 957-8588

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