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Hepatocellular Carcinoma Associated with Other Primary Malignancies

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THERE ARE several case reports about hepatocellular carcinoma (HCC) associated with second and even third primary malignancies [1] and two larger series [2, 3]. We report the occurrence of other primary malignancies in a series of 179 cases of HCC diagnosed in our unit from June 1981 to November 1989.

The diagnosis of HCC was suggested by ultrasound and confirmed by ultrasonically guided fine-needle biopsy [4] in 80% of cases and by laparoscopically controlled biopsy in 9%. In the remaining patients the diagnosis was made on the basis of ultrasonically detected focal liver lesions and by measurement of alpha-fetoprotein (AFP; Enzygnost-AFP): normal below 12 ng/ml, diagnostic above 500 ng/ml. In these patients impaired coagulation contraindicated biopsy.

Seventeen of the 179 patients with HCC (9.5%) had other cancers. One had two other primary malignancies: laryngeal cancer diagnosed 108 months before HCC and non-Hodgkin's lymphoma (NHL) simultaneously diagnosed. In the other 16 patients we found: NHL (3) and colon (2), rectal (1), breast (3), lung (1), gastric (2), uterine (1) and prostatic (2) cancers. One patient had Bowen's disease. In 14 of these 16 the discovery of the associated malignancy preceded that of HCC by several months (mean 46, range 3–120). In one patient the diagnoses were simultaneous and in another patient the diagnosis was made 22 months after that of HCC. The clinical and diagnostic features of these 17 cases of HCC were similar to those found in a larger series of HCC [5]. The pathological findings (evaluated in 15 cases) were: well differentiated HCC cells in seven cases, poorly differentiated cells in seven and pleomorphic large cells in one. The mean age at the time of diagnosis of HCC was 67 years (range 51–78). The male/female ratio was 1.8:1. Hepatic cirrhosis was present in 15 out of 17 patients. Only one patient was HBsAg positive and another six had HBs and/or HBe and/or HBc antibodies. AFP was diagnostic in seven patients.

The patient with two other tumours had been operated on for laryngeal cancer and was treated with chemotherapy for NHL. Four out of 16 patients with a tumour in addition to HCC had undergone chemotherapy for the associated cancer, five surgical removal, three surgery plus chemotherapy and one surgery plus radiotherapy. Two patients received hormonal therapy.

In the large Japanese series of 417 autopsy cases of HCC [6], 32 had associated cancers; three had multiple cancer. Associated cancers occurred in 5.8% of cases in 1967–74 and 8.3% in 1974–81. Cancers of the gastrointestinal tract comprised 56%. Only one case was associated with malignant lymphoma. Three cases had triple cancer. In the Hungarian series [2], nine out of 47 patients with HCC (19%) had an associated cancer (one of these had two other cancers). The most frequently associated tumour was renal cell carcinoma (three cases). One case of NHL was reported. Lin *et al.* from Taiwan [3], which is an area highly endemic for HCC, reported that 12 out of 562 patients (2.1%) had another malignancy. The most common second neoplasm was gastric cancer (eight cases). This tumour is the third most common neoplasm among men in Taiwan. However, the frequency in this series was so high that Lin *et al.* suggested a common environmental or genetic factor as promoter for HCC and gastric cancer. Only one patient had NHL.

In our series HCC was associated with a second malignancy in 9.5% of cases. The most commonly associated second neoplasm was NHL. HCC was the most frequently associated cancer in our previous series of 156 cases of NHL [7]. The association of HCC with NHL that we find probably reflects ascertainment bias in our institution. However, environmental or genetic factors could be causes.

Most patients developed HCC after another tumour and about half received chemotherapy. Could such drugs be carcinogenetic in the liver? Methotrexate is such a drug [8] but this agent was not used in our patients. Familial polyposis coli, which has neoplastic potential throughout the gastrointestinal tract [9], has been associated with HCC. HCC in this condition, in the absence of any other risk factor, has been considered a manifestation of the oncogenicity of the disease [10]. Familial polyposis coli was not found in our three patients out of five with gastrointestinal cancers who had colonoscopy.

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Erythema and Swelling of Ears After Treatment with Cytarabine for Leukemia

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COMMON side-effects of cytarabine plus an anthracycline for acute myelogenous leukemia (AML) include bone marrow depression, gastrointestinal symptoms, alopecia, fever and rashes [1–3]. Burgdorf *et al.* described an acral erythema in a patient receiving high-dose chemotherapy [4]. The syndrome consists of pain and dysesthesia of palms and soles, erythematous discoloration, bulla formation and desquamation [5–9]. Clinical and histopathological features are consistent with a toxic eruption [8].

Over a 3 year period, eight patients with acute myelogenous leukemia treated with combination chemotherapy had painful erythema and swelling of the ears (Table 1). Infectious causes could be ruled out. The symptoms subsided spontaneously within a week. Consolidation therapy with the same drugs had no skin complications, except in patient 7.

Table 1. Details of patients

Patient	Cytostatic drugs	Day of symptoms
1 (38/F)	Cytarabine 100 mg/m² Vincristine 2 mg 1 day Doxorubicin 45 mg/m²	6
2 (64/F)	Cytarabine 200 mg/m² Doxorubicin 30 mg/m²	5
3 (59/F)	Cytarabine 200 mg/m² Doxorubicin 45 mg/m²	7
4 (50/F)	Cytarabine 200 mg/m² Doxorubicin 45 mg/m²	4
5 (43/F)	Cytarabine 200 mg/m² Doxorubicin 45 mg/m²	8
6 (47/F)	Cytarabine 2 g/m² *m*-Amsacrine 120 mg/m²	7
7 (58/M)	Cytarabine 1 g/m² *m*-Amsacrine 120 mg/m²	18*
	Cytarabine 4 g/m²	3
8 (52/M)	Cytarabine 200 mg/m² Doxorubicin 45 mg/m²	6

Cytarabine, doxorubicin and *m*-amsacrine for 7, 3 and 3 days, respectively, except in patients 6 (cytarabine for 6 days) and 7 (cytarabine for 6 days and then for 4 days at higher dose during second consolidation cycle). Patients 2, 3 and 5 also had erythema of the trunk, legs, hands and/or face.
*Erythema of face.

All our patients had been treated for AML with cytarabine in combination with either daunorubicin or *m*-amsacrine. All patients received alimentary tract decontamination with neomycin, polymyxin B, amphotericin B and nalidixic acid or pipemidic acid [10]. Allopurinol and sodium bicarbonate were administered routinely during cytostatic treatment. During or soon after cytostatic treatment, both ears were red and swollen. Because the earlobes were also involved, this condition could be distinguished from acute perichondritis. All the patients had a normal temperature. Because of the risks of bleeding and secondary infection, biopsies were not done. Patients 3 and 4 received high-dose corticosteroids prophylactically. The side-effect is probably the result of a toxic reaction because in patients 2, 3, 5 and 7, other parts of the body were also involved.

It is most likely that cytarabine was responsible for this reaction although drugs such as nalidixic acid or allopurinol might have been involved.

Although corticosteroids may be therapeutic and prophylactic in cytarabine-induced skin toxicity [2, 3], their value is not established. Cytarabine can be re-instituted with little hazard; in our group, consolidation therapy induced the same side-effect in only one patient.

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