Hepatitis-Associated Antigen in Patients with Cancer

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The hepatitis-associated antigen (HAA) (Australian antigen) is either the infective agent of viral hepatitis or a virus-related protein(1). It is present in the blood during the incubation period and early clinical course of acute viral hepatitis in adults(1,2). The presence of the HAA in Krugman's long incubation hepatitis (MS-2) and its absence in childhood hepatitis, epidemic hepatitis, and in short incubation hepatitis (MS-1) indicates it is associated with the serum hepatitis virus (s)(2,3). The antigen persists for longer periods in the blood of some patients with chronic active hepatitis(4,5) and dialysis-associated hepatitis(6). It is frequently present in the serum of patients with Down's syndrome(7), lepromatous leprosy(8) and certain types of leukemia(7,9–11).

We have investigated the frequency of HAA in the sera of patients with a wide spectrum of neoplastic diseases, including primary and metastatic liver neoplasms. Many of the patients studied had received multiple transfusions and were being treated with immunosuppressant drugs.

METHODS

Sera Samples. Sera were obtained from 789 patients with biopsy proven neoplastic diseases in a number of institutions including Memorial Hospital for
Cancer and Allied Diseases, M. D. Anderson Hospital and from patients with hepatoma in Uganda. Sera were stored at -20°C. The African patients with hepatoma have been described in detail elsewhere(12). Age, sex, medical, and transfusion history were noted on all patients. Data was statistically analyzed using the chi-square test with Yates correction.

*Immunodiffusion Technique.* All sera were tested for the presence of HAA by the micro-Ouchterlony immunodiffusion technique described previously(1). The antisera employed (serum S) were 4-fold concentrated serum from a multiply transfused patient with hemophilia(1).

**RESULTS**

*Positive Sera.* Twelve of 789 sera samples were positive for HAA (Table 1). The highest incidence of positive sera occurred in patients with liver cancer (4.3%), breast cancer (2.8%), and in patients with multiple myeloma (2.4%).

Two patients with HAA (breast, Hodgkin's Disease) had clinically suspected, but not biopsy proven, posttransfusion hepatitis. Four additional patients (breast cervix, hepatoma, and myeloma) had a history of multiple transfusions. The remaining patients with detectable antigen had no history of previous transfusions of blood products, shared needles, shellfish ingestion or close exposure to pa-

**TABLE 1**

| Neoplasm                  | No. positive/no. tested | % Positive |
|---------------------------|-------------------------|------------|
| Breast                    | 2/71                    | 2.8        |
| Choriocarcinoma           | 0/5                     | 0          |
| Gastrointestinal          | 0/49                    | 0          |
| Genitourinary             | 0/17                    | 0          |
| Gynecological             | 1/116                   | 0.8        |
| Leukemia                  | 1/119                   | 0.8        |
| Liver, hepatocarcinoma    | 4/89                    | 4.4        |
| Liver, cholangiocarcinoma | 0/5                     | 0          |
| Lung                      | 0/31                    | 0          |
| Lymphoma                  | 1/117                   | 0.8        |
| Melanoma                  | 0/9                     | 0          |
| Multiple myeloma          | 3/124                   | 2.4        |
| Oro–naso–pharynx          | 0/11                    | 0          |
| Polycythemia              | 0/3                     | 0          |
| Sarcomas                  | 0/10                    | 0          |
| Skin                      | 0/7                     | 0          |
| Thyroid                   | 0/4                     | 0          |
| Miscellaneous             | 0/2                     | 0          |
| **Total**                 | **12/789**              | **1.5**    |
| Normal Controls, USA†     | 22/27,387               | 0.08       |
| Normal Controls, Uganda†  | 6/311                   | 1.9        |

*† Randomly selected, healthy individuals.*
tients with hepatitis. They had all received parenteral injections of medication. One of 24 patients with chronic lymphocytic leukemia had detectable serum antigen. He had not received transfusions and had normal liver function tests. No other patients with leukemia had detectable antigen. Ten of the 12 patients with detectable antigen had normal liver function tests. There appeared to be no relationship between age of the patient and occurrence of antigen.

Primary and metastatic liver neoplasms. Four of 94 patients with primary liver cancer had detectable HAA. The incidence of antigen in patients with hepatocarcinoma in Uganda (3/34, 8.8%) was considerably higher than that detected in well individuals in that country (6/311, 1.9%), however not significant at the 5% level (.1 > p > .05). None of the African patients with detectable antigen had received blood transfusions. The one positive American patient with hepatocarcinoma had received 4 units of blood, fourteen days before detection of the antigen in his blood. It should be noted that the incidence of HAA in well individuals in Uganda (1.9%) is significantly higher than for similar individuals in the United States (22/27, 387; 0.08%)(2).

Eighty-seven patients had abnormal liver function tests associated with biopsy or liver scan documented liver metastases. None of these patients with liver metastases had detectable HAA.

Additional clinical data. One hundred thirty patients received blood transfusions (average: 6 units/patient) within 6 months of having their blood tested for HAA. Thirty-two of these patients received transfusions (average: 4.1 units/patient) in the week before having the serum sample drawn. Four of the 130 transfused patients were positive for HAA.

The HAA was not found in 174 patients who were receiving cytotoxic drug or prednisone therapy for at least two weeks. 78 of the patients receiving drug therapy had total white counts below 5000/mm³ and 28 patients had white counts below 2500/mm³ as a result of therapy.

DISCUSSION

With the exception of African patients with hepatocarcinoma, there was no suggestion of a correlation between cancer type and presence of HAA. Previous studies have shown an increased incidence of Australian antigen in patients with leukemia, especially of the acute granulocytic, acute lymphocytic, and chronic lymphocytic types(9-11). Our findings do not confirm this association. Only one of 119 leukemic patients had detectable antigen. This group included 26 patients with acute granulocytic and 34 patients with acute lymphocytic types, most of whom had received multiple transfusions and were receiving aggressive cytotoxic drug therapy. One of 24 patients with chronic lymphocytic leukemia had detectable antigen. It should be noted that our series of leukemic patients is smaller than those previously reported demonstrating a higher incidence of HAA.

As stated in the introduction, HAA is found only transiently in the blood of patients with acute viral hepatitis, but it persists in some patients with chronic
active hepatitis(4,13,15) and chronic anicteric viral hepatitis. A number of clinicopathological studies have demonstrated that chronic anicteric hepatitis can be a precursor of cirrhosis(16,17). Because approximately two-thirds of patients with hepatoma also have cirrhosis, usually of the “postnecrotic” type, it is of importance to determine the role of the hepatitis virus in the pathogenesis of primary liver cancer(12,18). It has been postulated that the high incidence of hepatitis and other causes of liver impairment in Africa, predispose affected individuals to the effects of chemical hepatocarcinogens (e.g., mycotoxins)(19). Smith and Blumberg(20) studied 65 patients with hepatoma from Asia, Africa, and the United States and found the incidence of antigen in the hepatoma patients no greater than in the controls. However, three studies have shown a relationship between hepatocellular carcinoma and the HAA in three different areas of the world(21–23). Vogel’s series from Uganda demonstrated the antigen in 18 of 45 patients with hepatocellular carcinoma. The antigen tended to occur in younger patients in that series. In our study only one of 55 non-African patients with hepatoma had detectable antigen and he had received blood transfusions. However, the incidence of HAA in the Ugandan hepatoma patients (8.8%) was considerably higher than in the control population, (1.9%), although not significant at the 5% level. The number of patients studied was small and the controls were nonhospitalized well individuals and, therefore, not strictly comparable. However, these results would indicate further studies are necessary, specifically examination of hepatoma tissue for the presence of intracellular antigen and the study of larger numbers of patients with hepatoma and well chosen control sera.

It has been postulated that the frequency of the antigen carrier state in patients with Down’s syndrome, lepromatous leprosy, and leukemia is caused by the altered host defense mechanisms found in these patients(7,10,24). Most certainly a number of our patients had altered immune status both as a result of immunosuppressant drug therapy and because of primary hematopoietic malignancy. Examining single serum specimens with a relatively insensitive technique, it appears that this type of immune suppression does not predispose to the HAA carrier state even though this group of patients receives frequent transfusions. Although additional positive sera may be obtained by serial sample collections, it is unlikely that a more sensitive test system (e.g., complement fixation) would detect more HAA carriers(25).

**SUMMARY**

The sera of 789 patients with neoplastic diseases were studied for the presence of hepatitis-associated antigen (HAA) using an immunodiffusion technique. Twelve patients had detectable serum antigen. Six of the twelve had acute viral hepatitis or had received transfusions. There was no strong correlation between cancer type and detectable antigen. The frequency of HAA in African patients with hepatoma was higher than in controls, but was not significant at the 5%
level. One of 119 patients with leukemia had detectable antigen. In examining single serum specimens using a relatively insensitive technique, we could not detect an antigen carrier state in patients with hematopoietic malignancies even though they were subjected to immunosuppressive drug therapy and frequent blood transfusions.

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