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SERUM α-FETOPROTEIN IN HEPATOMA PATIENTS AFTER LIVER TRANSPLANTATION

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α-1-Fetoprotein (AFP) was measured in the sera of 5 hepatoma patients following total hepatectomy and orthotopic liver transplantation. Immunosuppressive therapy, rejection episodes, and infection did not alter the serum level of AFP. Low AFP levels persisting posttransplantation indicated the presence of slow-growing residual tumor in 3 patients. A sharp increase in serum AFP levels preceded clinical evidence of rapid tumor growth in 1 patient. Disappearance of AFP in 1 patient who is still symptom-free after 9 months suggests little or no residual tumor. Serial AFP levels can be helpful in assessing the results of therapeutic attempts in patients with liver carcinoma.

Human α-fetoprotein (AFP) is a unique fetal α-1 globulin which reappears in the serum of most patients with carcinoma of the liver and has been shown to be diagnostic of this malignancy in the adult.[1-5] The serum concentration of AFP has been found to stabilize or generally increase with progression and growth of the tumor.[4, 6] In this study we have examined the changes in the serum concentration of AFP after autologous liver transplantation in 5 patients with hepatoma in an effort to assess the value of AFP in predicting tumor residual or recurrence.

Methods

Monospecific antisera to AFP were raised in rabbits according to previously published methods and shown to be monospecific by double immunodiffusion, immunoelectrophoresis, and counterimmunoelectrophoresis.[6] AFP was quantitated in hepatoma serum pool according to the method of Gitlin et al.[7] and used as a standard. Sera were assayed for AFP by radial immunodiffusion,[8] modified to increase its sensitivity.[9] The lower limit of sensitivity of this method was found to be approximately 1 mg per 100 ml. Serum concentrations of AFP between 1 mg per 100 ml and 0.025 mg per 100 ml were measured by serial dilutions and by performing counterimmunoelectrophoresis.[6] Sera were shipped frozen in Dry Ice and stored at −70 C until studied. Further details of the clinical course of the patients described have been published.[10]

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Case 1

Explosive tumor growth (fig. 1). A 16-year-old male (OT-23[10]) with primary carcinoma of the liver underwent total hepatectomy with orthotopic liver transplantation on November 10, 1968. A very mild rejection episode in the 2nd week reversed with increasing the immunosuppressive drug dosages (see fig. 1). The preoperative AFP level of 78.5 mg per 100 ml fell to 2 mg per 100 ml 11 days posttransplantation. The patient was discharged, apparently free of disease 5 weeks posttransplantation, although a low level of AFP persisted. Three weeks later

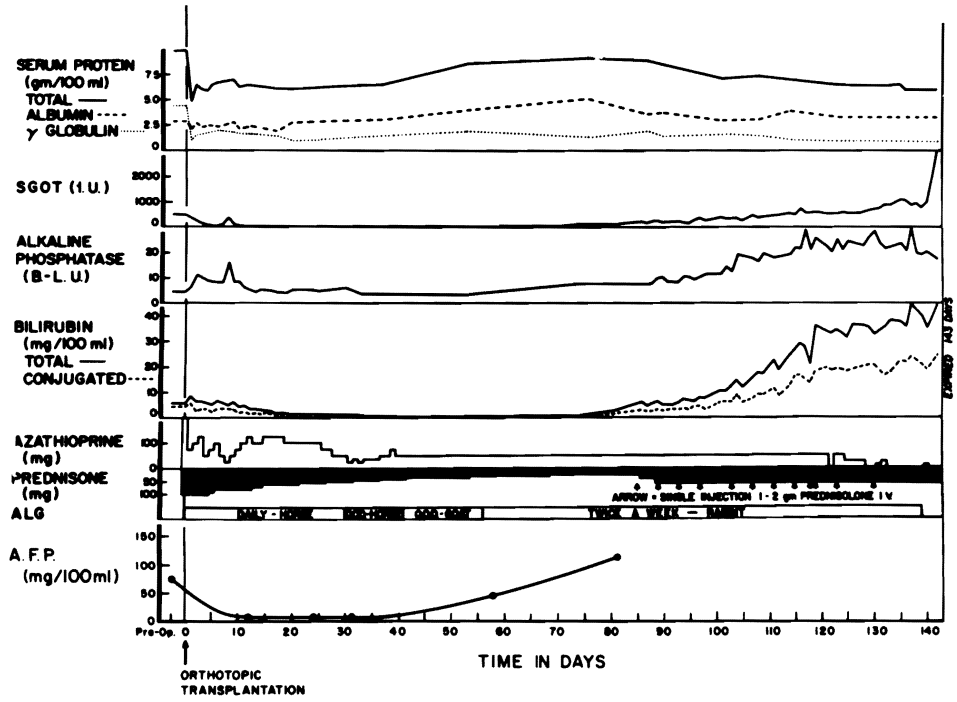

FIG. 1. Case 1, A 16-year-old male with explosive tumor growth after liver transplantation.

the AFP level rose to 44 mg per 100 ml and subsequently, progressive bilirubinemia and deterioration of liver function developed. The AFP serum concentration reached 110 mg per 100 ml as serial liver scans demonstrated an explosive tumor growth with a rapid increase in liver size and increasing "cold" areas during the last 2 months of life. At autopsy the homograft liver was virtually replaced with recurrent hepatoma.

Case 2

Slow-growing tumor recurrence with chronic transplant rejection (fig. 2). A 16-year-old female (OT-14[10]) with hepatoma underwent orthotopic transplantation on March 16, 1968. The hepatic function became abnormal over the 1st few weeks but responded to immunosuppressive therapy. Subsequently, during the following year a chronic rejection process occurred with deepening jaundice. Throughout this entire period the AFP level remained at 4 to 5 mg per 100 ml. A second transplantation was performed after 380 days, prior to which metastases could not be found. At reoperation, there was extensive tumor involving the posterior diaphragm, several ribs, the pancreas, and the extraperitoneal space. A very small recurrence was present in the rejected homograft. The patient lived for 2 months after retransplantation and finally died of carcinomatoses and intraperitoneal infection. In this patient, the presence of detectable AFP correctly identified the presence of recurrent tumor for almost 1 year before this could be proven histopathologically.

Case 3

Moderately rapidly growing tumor recurrence after transient rejection (fig. 3). A 44-year-old male (OT-15[10]) with hepatoma underwent orthotopic liver transplantation on April 14, 1968. His AFP level of 5 mg per 100 ml fell postoperatively to 1 to 2 mg per 100 ml. During the 1st few weeks postoperatively, he passed through an acute rejection crisis with no change in the persistently low level of AFP. He then did well, apparently free of disease, for more than 9 months with the AFP levels falling to undetectable amounts even though there was evidence by chest X-ray of pulmonary metastases. In the 9th postoperative month the AFP level rose to 4.8 mg per 100 ml just prior to the reappearance of jaundice, which fluctuated with other abnormalities of liver function. An area of decreased uptake on liver scan became evident at the hilum of the liver. Several positive blood cultures suggested liver abscess or

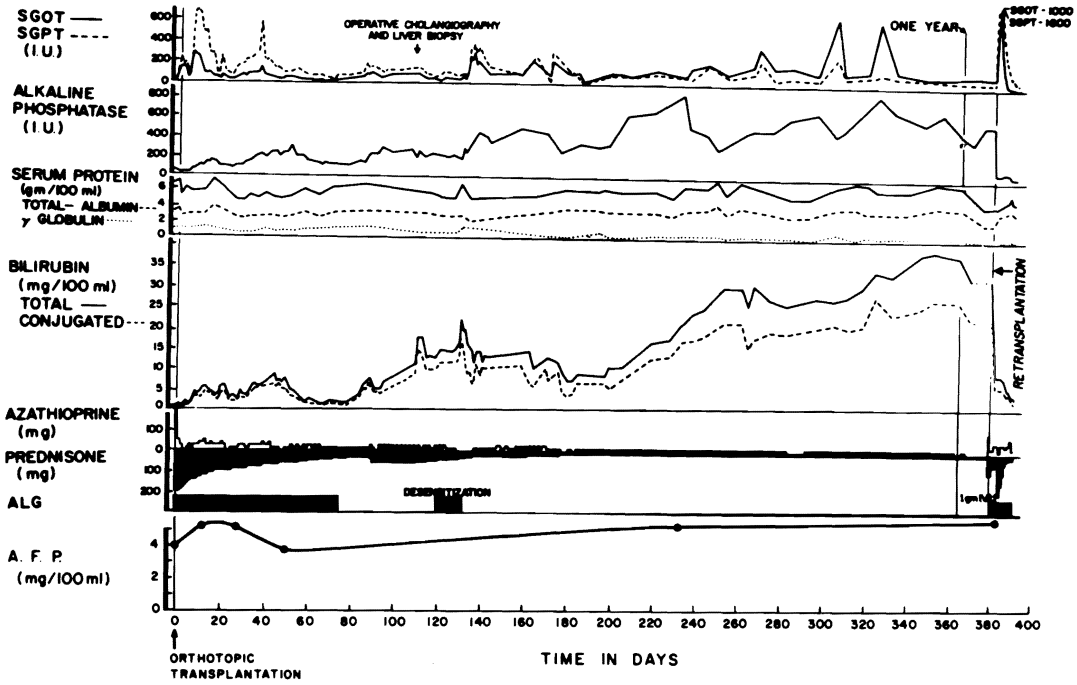

FIG. 2. Case 2, A 16-year-old female with chronic transplant rejection and slow-growing tumor recurrence.

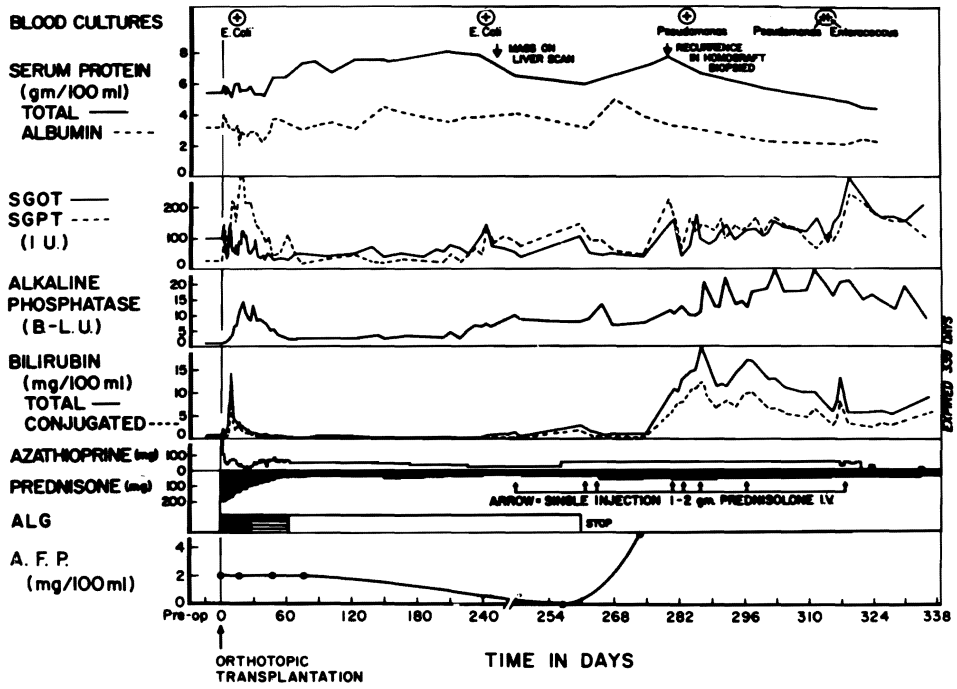

FIG. 3. Case 3, A 44-year-old male with a moderately rapidly growing tumor recurrence after a transient rejection episode.

septic infarction and exploration was performed. At operation, although no tumor was visible in the liver, a needle biopsy into the suspicious area revealed recurrent carcinoma. At autopsy 2 months later, a tumor 10 cm in diameter was noted at the hilum infringing on the common duct and causing partial obstruction and cholangitis. An even larger tumor nodule of 13 cm diameter, which had not been suspected on liver scan, was found in the center of the right lobe. Extensive metastases were also found in the lungs. In this patient, the fluctuating AFP levels did not reflect the persistant pulmonary mestases noted on chest X-ray, but appeared to reflect the recurrent hepatic tumor.

Case 4

Slow growing tumor recurrence. A 10-year-old female (OT-26[10]) with hepatoma underwent orthotopic liver transplantation on May 11, 1969. Although AFP was undetectable preoperatively, a low level of 2 to 3 mg per 100 ml was demonstrable 1 week after transplantation. Six weeks postoperatively, a metastasis was noted radiologically in the left upper lobe of the lung. She died of varicella infection 2½ months later, and no other metastasis was found at autopsy. In this patient, the persistent AFP level did indicate the presence of a small metastatic focus.

Case 5

Possible cure. A 4-year-old female (OT-27[10]) with biliary atresia had an orthotopic liver transplant on January 25, 1970. Examination of the excised liver unexpectedly revealed a hepatoma, 2 cm in diameter. After transplantation a low level of 4 to 6 mg per 100 ml of AFP persisted unchanged for about 1 month. Four months postoperatively AFP levels were < 0.1 mg per ml, and after 3 more months AFP became undetectable. More than 10 months post-transplantation she is clinically well without signs of recurrence.

Discussion

α-1-Fetoprotein, an α-1 globulin normally found only in fetal serum,[7] reappears in the serum of patients with hepatocellular carcinoma.[1-6] This serum protein is synthesized only by embryonic liver cells and malignant liver cells and not by any other human tissue.[11] It is detectable in the serum of 50 to 95% of hepatoma patients[1-6] depending on their ethnic origin[6] and not in any other benign or malignant condition, except in the sera of about one-third of children with embryonal teratoblastomas.[2] Therefore, the presence of this fetal protein in adult sera has been considered to be diagnostic of hepatocellular carcinoma. The serum concentrations vary widely and do not appear to have any clinical significance in any individual case.[4, 6] However, the level tends to stabilize or increase in the serum of untreated hepatoma patients,[4, 6] falling in some patients only terminally.[6, 12] Purves et al.[12] reported that systemic chemotherapy had no significant effect on either the tumor or serum AFP levels. Our studies of patients who underwent liver transplantation suggest that serum AFP levels were apparently unaffected by immunosuppressive therapy, acute and chronic transplant rejection, or intercurrent infections (cases 1 to 4). Hepatic necrosis during rejection episodes did not alter the AFP levels. This indicates that AFP is not an acute phase reactant, even in an AFP-producing hepatoma. However, changes in the serum concentration generally appear to correlate with tumor growth rate, as suggested by previous clinical studies[6] and strikingly illustrated in case 1.

Serum proteins have a rapid degradation rate after liver transplantation[10] and renewed synthesis reflects the donor genetic pattern within days or weeks.[10, 13] The rapid disappearance of AFP, suggesting a short metabolic half-life, was illustrated in case 1 where serum AFP concentration fell from a preoperative 78 mg per 100 ml to 2 mg per 100 ml 11 days after hepatectomy. Therefore, the slow disappearance of serum AFP in case 5 suggested that viable tumor cells persisted after transplantation. The host-immune response may have finally destroyed the last few tumor cells. This patient is clinically well now, 10 months after transplantation, and is still being closely followed.

These studies strongly suggest that serial AFP serum levels are a helpful prognostic guide in assessing residual or recurrence of tumor after therapeutic attempts such as liver transplantation.

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