Digestive Diseases and Sciences, Vol. 46, No. 8 (August 2001), pp. 1709–1713

Clinical Significance of Elevated α-Fetoprotein in Adults and Children

RANDEEP KASHYAP,* ASHOK JAIN, MD,* MICHAEL NALESNIK,† BRIAN CARR,* JACKIE BARNES,* HUGO E. VARGAS,‡ JORGE RAKELA,‡ and JOHN FUNG*

The aim of the current study is to identify underlying pathology associated with elevated serum α-fetoprotein (AFP; >20 ng/ml) among patients referred to a tertiary-care academic medical center with emphasis in liver diseases, hepatobiliary surgery, and liver transplantation. From May 1992 to April 1997, 386 patients (320 adults and 66 children) with elevated AFP (>20 ng/ml) were identified from the Medical Archival System (MARS) database at the University of Pittsburgh Medical Center. The medical records from all these patients were retrospectively reviewed. Radiological, pathological, and biochemical profiles were obtained at the time of documented elevated AFP. These patients included: 218 adults with malignancies, 102 adults without malignancies, 18 children and infants with malignancies, and 48 children and infants without malignancies. Thirty-two percent of adults were found to have raised AFP with liver disease and without hepatocellular carcinoma and 78% had some type of malignancy, predominantly hepatocellular carcinoma. Seventy-three percent of infants and children had elevated AFP without malignancy. Based on our findings, we recommend that all patients (adults, infants and children) with raised AFP of >20 ng/ml should undergo thorough evaluation to rule out malignant disease.

KEY WORDS: α-fetoprotein; hepatocellular carcinoma; malignancy; liver disease.

The biological significance and mechanism of the reexpression of α-fetoprotein (AFP) in hepatocellular carcinoma (HCC) and other neoplastic processes are unclear (1, 2). The significance of elevated AFP in nonneoplastic disease is even less well understood (3, 4). Normally, AFP is a fetal serum protein. Elevated serum levels of AFP have been well documented in pregnancy and in yolk sac tumors. It has also been found in newborns and infants (age <1 year), in adults with HCC, and in children with hepatoblastoma. While elevated serum levels of AFP have been reported in patients with nonneoplastic liver disease in adults and children >1 year of age, these cases are sparse and the significance of increased AFP has not been determined. The aim of the current study is to identify possible etiologic factors and their significance in patients who were found to have elevated serum AFP (≥20 ng/ml) in a tertiary referral academic medical center.

MATERIALS AND METHODS

From May 1992 to April 1997, 6627 patients had 11,444 AFP determinations recorded in the Medical Archival System (MARS) database of the Thomas E. Starzl Transplantation Institute at the University of Pittsburgh Medical Center. Thus academic medical center has a large referral practice for hepatobiliary diseases and does not include an obstetrical facility. All clinical data related to history, physical examination, progress notes, and operative reports, as well as radiological, pathological, and laboratory data from patients are continuously fed into MARS. The records from

Manuscript received February 23, 1999; revised manuscript received January 8, 2001; accepted January 24, 2001.

From the *Thomas E. Starzl Transplantation Institute, Department of Surgery; †Department of Pathology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania; and ‡Department of Medicine, Mayo Clinic Scottsdale, Scottsdale, Arizona.

This paper was presented at the American Association for Liver Diseases, Chicago, November 1997.

Address for reprint requests: Dr. Ashok Jain, 4C Falk Clinic, 3601 Fifth Avenue, Pittsburgh, Pennsylvania 15213.

TABLE 1. ELEVATED AFP IN ADULTS (N = 320)*

	HCC	*Cholangio CA*	*Testicular CA*
Adults with malignancies (N = 218)			
Number	211	4	3
Age (yr)	59.3	59.2	23.3
Sex: M/F	159/56	2/2	3/0
AFP (ng/ml)			
Mean ± SD	1030 ± 1890	292 ± 301	3325 ± 4466
Median	128	295	1356
Range	20–9661	20–557	183–8438
	HCV	*HBV*	*Other liver diseases*
Adults with hepatic diseases (N = 102)			
Number	80	10	12
Age (yr)	52.1	47.4	57.4
Sex: M/F	56/24	6/4	7/3
AFP (ng/ml)			
Mean ± SD	127 ± 438	48 ± 29	119 ± 166
Median	41	45	50
Range	20–3268	20–120	20–470
T.Bili (mg/dl)	5.1 ± 2.3	1.9 ± 1.0	2.7 ± 2.0
AST (units/liter)	166 ± 163	82 ± 56	113 ± 68
ALT (units/liter)	133 ± 85.5	81 ± 55	91 ± 76

*AFP = α-fetoprotein, AST = aspartate aminotransferase, ALT = alanine aminotransferase, T.Bili = total bilirubin, HBV = hepatitis B virus, HCV = hepatitis C virus, CA = carcinoma, HCC = hepatocellular carcinoma, AST and ALT normal values < 40 units/liter

all the patients with elevated AFP (>20 ng/ml) were retrospectively reviewed to the time of documented elevated AFP. Radiological investigations included computed tomography (CT) and/or magnetic resonance imaging (MRI) and/or ultrasound examination. Liver biopsies and/or hepatectomy specimens from transplant patients were obtained for confirmation of diagnosis. Laboratory tests included liver injury tests and serologic markers for hepatitis B and C viruses. Patients were divided on the basis of age into adult (≥18 years old) or pediatric (<18 years old) groups. The pediatric population was also further divided into two subgroups, infants (≤1 year old) or children (>1 year old). The three age groups were further subdivided into those with or without malignant conditions.

RESULTS

From a total of 6627 patients, 386 (5.8%; 320 adults and 66 pediatric patients) were found to have elevated AFP (≥20 ng/ml) at the time of their initial evaluation and these patients were grouped as follows.

Adults with Malignancies (N = 218). Two hundred eighteen (68%) adults had documented evidence of a malignancy. Two hundred eleven patients had HCC, 4 had cholangiocarcinoma (cholangiocarcinoma in two patients, cholangiocarcinoma with hepatic metastasis in 1, cholangiocarcinoma with primary sclerosing cholangitis in 1), and 3 patients had a testicular mixed germ-cell tumor. The diagnoses were confirmed by histopathologic analysis of liver tissue. The characteristics of these patients and their AFP levels are shown in Table 1.

Adults Without Malignancies (N = 102). The remaining 102 adult patients did not have any malignancy but had documented liver disease (Table 1). Hepatitis C virus infection was positive in 80 cases (78.4%) with 61 having cirrhosis and 19 having chronic hepatitis without cirrhosis. Two patients with chronic hepatitis had incidental prior history of carcinoma of prostate and carcinoma of the breast without signs of recurrence. Hepatitis B virus infection was positive in 10 cases (9.8%), and 12 cases (11.7%) had other forms of chronic liver diseases (alcoholic in 3 patients, hemochromatosis in 2, and cryptogenic in 7).

Thirty of the 80 patients had repeated determinations of AFP levels and at least one CT and/or MRI examination every year and had no evidence of HCC during subsequent follow-up. One patient was found to have an undiagnosed HCC on histologic examination of explant one year after the initial elevated AFP of 393 ng/ml was detected.

Children and Infants with Malignancies (N = 18). Eighteen (27.3%) of 66 pediatric patients had documented evidenced of malignancy (Table 2). Ten (1 infant and 9 children) had hepatoblastoma and 8 (6 infants and 2 children) had nonhepatic malignancies (sacrococcygeal teratoma in 3 patients, testicular tu-

TABLE 2. ELEVATED AFP IN PEDIATRIC POPULATION ($N = 66$)

	Hepatoblastoma (N = 10)	
	Infants (N = 1)	*Children* (N = 9)
Mean Age (yr)	0.14	4.7
Sex: M/F	0/1	4/5
AFP (ng/ml)		
Mean ± SD	235	4826 ± 3923
Median		4874
Range		49–9934

Nonhepatic malignancies (N = 8)

Patient	*Age (yr)*	*Gender*	*AFP*	*Diagnosis*
1	0.34	M	53	?Melanotic neuroectodermal tumor
2	0.61	M	75	?Melanotic neuroectodermal tumor
3	0.01	M	23	Sacrococcygeal teratoma
4	1.03	M	20	Sacrococcygeal teratoma
5	0.39	M	34	Sacrococcygeal teratoma
6	1.0	M	51	Testicular tumor
7	0.13	M	148	Testicular tumor
8	14.3	F	127	Ovarian carcinoma

	Hepatic diseases (N = 29)	
	Infants (N = 19)	*Children* (N = 10)
Mean Age (yr)	0.5	4.1
Sex: M/F	11/8	5/5
AFP (ng/ml)		
Mean ± SD	1307 ± 1702	316 ± 406
Median	137	93
Range	23–4554	24–1019
T.Bili (mg/dl)	9.28	7.07
AST (U/l)	117.6	447
ALT (U/l)	85.9	326
GGTP (U/l)	30460	110.2

	Nonhepatic diseases (N = 19)	
	Infants (N = 14)	*Children* (N = 5)
Mean Age (yr)	0.5	2.3
Sex: M/F	11/3	2/3
AFP (ng/ml)		
Mean ± SD	831 ± 2120	2351 ± 4271
Median	78	298
Range	20–8076	58–8752

mor in 2, probable melanotic neuroectodermal tumor in 2, and ovarian cancer in 1). All diagnoses were based on histologic examination.

Children and Infants Without Malignancies ($N = 48$). The remaining 48 (72.7%) infants and children did not have malignancy but had other hepatic and nonhepatic diseases (Table 2). Twenty-nine patients (19 infants and 10 children) had an underlying hepatic disease and 19 (14 infants and 5 children) had a nonhepatic disease. Among 29 patients with hepatic diseases, 22 (18 infants and 4 children) had biliary atresia, 3 (1 infant and 2 children) had chronic hepatitis, 3 children had metabolic liver diseases (glycogen storage type-1 V), and 1 child had liver failure of indeterminate etiology. Among 19 patients without hepatic disease, 6 (5 infants and 1 child) had intestinal atresia, 5 infants had congenital hemihypertophy, 3 (1 infant and 2 children) had spinocerebellar disease, and 5 (3 infants and 2 children) had other congenital

diseases (diffuse cutaneous and hepatic hemangioma in one patient).

DISCUSSION

Elevated AFP levels are found during pregnancy as the fetal gastrointestinal tract contributes to AFP levels in the amniotic fluid and hence to those in maternal serum (5–7). AFP is present at birth and declines to less than 10 ng/ml within 300 days (2). Its importance for the diagnosis and clinical management of HCC and yolk sac tumor is well recognized (8–13). AFP elevation as a useful marker of HCC was first established in carriers of hepatitis B surface antigen (11, 12). In the present study there were malignant and nonmalignant conditions apart from HCC and yolk sac tumors that were associated with increased AFP in adults and children. AFP-producing tumors other than HCC and yolk sac tumors are rare occurrences (14, 15). Waldman and McIntire (14) reported an association of raised AFP levels with malignancies of stomach, colon, pancreas, and lung. Interestingly, in our study, two patients with chronic hepatitis had underlying malignancies other than HCC or testicular mixed germ-cell tumor; one patient had a prostatic cancer and the other had breast cancer. An increased AFP level is also documented with viral hepatitis and liver cirrhosis without evidence of HCC (16, 17). Among our 102 adult patients without malignancies, hepatitis C virus infection was detected in 80 cases (78.4%). Patients with hepatitis and cirrhosis may also have elevated AFP due to hepatic regeneration (18).

Tsukuma *et al* reported the cumulative lifetime risk of liver cancer in cirrhotic patients as 12.5% and somewhat lower (3.8%) in noncirrhotic hepatitis patients (19). In our study, 102 adults with underlying liver disease did not develop HCC during their follow-up; 30 had completed at least five years of follow-up, while 72 patients had less than five years follow-up. Only one of the patients who underwent liver transplantation was found to have an incidental HCC in his original liver on histologic examination.

Elevated AFP levels are reported during pregnancy (5, 6); however, since our institution does not have obstetrical facilities, we did not find pregnancy as a cause of raised AFP. In infants and children, serum AFP can be elevated in a number of conditions besides biliary atresia and hepatoblastoma. This view is supported by the observation that fetal stomach, intestines, and yolk sac, in addition to the fetal liver, synthesize AFP (14).

Based on our findings, we recommend that all patients (adults, children, and infants) with raised AFP of >20 ng/ml undergo a thorough evaluation to look for an underlying malignant condition, recognizing that this condition does not necessarily originate in the liver. All patients with elevated AFP should be studied initially at least with a chest and abdominal CT scan, and suspicious hepatic lesions should be evaluated with a CT arteriogram/portogram. However, it is clear from this study that a significant number of patients with various nonmalignant diseases may have elevated AFP, and some patients with an underlying liver disease may have elevated AFP without an associated hepatic malignancy.

REFERENCES

1. Abelev GT, *et al*: Embryonal serum alpha-globulin in cancer patients: Diagnostic value. Int J Cancer 2(5):551–558; 1967
2. Kew MC: Hepatocellular carcinoma. Postgrad Med J 59(Suppl 4):78–87, 1983
3. Tsuchida Y, *et al*: Evaluation of alpha-fetoprotein in early infancy. J Pediatr Surg 13(2):155–162, 1978
4. Alpert E, Feller ER: Alpha-fetoprotein (AFP) in benign liver disease. Evidence that normal liver regeneration does not induce AFP synthesis. Gastroenterology 74(5, Pt 1):856–858, 1978
5. Malek A, Sager R, and Schneider H: Transport of proteins across the human placenta. Am J Reprod Immunol 40(5):347–351, 1998
6. Richardson BE, *et al*: Levels of maternal serum alpha-fetoprotein (AFP) in pregnant women and subsequent breast cancer risk [see comments]. Am J Epidemiol 148(8):719–727, 1998
7. Van Rijn M, *et al*: Maternal serum alpha-fetoprotein in fetal anal atresia and other gastro-intestinal obstructions [see comments]. Prenat Diagn 18(9):914–921, 1998
8. Barroso A, Alpert E: Diagnostic procedures in the evaluation of hepatic diseases. Functional evaluation: Carcinoembryonic antigen (CEA) and alphafetoprotein (AFP) as tumor markers of the liver. Lab Res Methods Biol Med, 7:153–157, 1983
9. Trichopoulos D, *et al*: Alphafetoprotein levels of liver cancer patients and controls in a European population. Cancer 46(4):736–740, 1980
10. Chan SH, *et al*: Comparison of various assays for detection of AFP in differentiating patients with primary hepatocellular carcinoma from controls. J Clin Pathol 33(8):792–793, 1980
11. Adinolfi M: Human alphafetoprotein 1956–1978. Adv Hum Genet 9:165–228, 1979
12. Chen DS, Sung JL: Serum alphafetoprotein in hepatocellular carcinoma. Cancer 40(2):779–783, 1977
13. Eleftheriou N, *et al*: Proceedings: Serum alphafetoprotein levels in liver disease: Relation to hepatocellular regeneration and development of hepatoma. Gut 16(10):835, 1975
14. Waldman TA, McIntire KR: The use of a radioimmunoassay for alpha-fetoprotein in the diagnosis of malignancy. Cancer 34(4, Suppl):1510–1515, 1974

15. McIntire KR, *et al*: Simultaneous radioimmunoassay for carcinoembryonic antigen (CEA) and alpha-fetoprotein (alphaFP) in neoplasms of the gastro-intestinal tract. Ann Clin Lab Sci 4(2):104–108, 1974
16. Furukawa, R, *et al*: Clinical significance of serum alpha-fetoprotein in patients with liver cirrhosis. Tumor Biol 5(6):327–338, 1984
17. Di Bisceglie AM, Hoofnagle JH: Elevations in serum alpha-fetoprotein levels in patients with chronic hepatitis B. Cancer 64(10):2117–2120, 1989
18. Rakela J, *et al*: A double-blinded, randomized trial of hydrocortisone in acute hepatic failure. The Acute Hepatic Failure Study Group. Dig Dis Sci 36(9):1223–1228, 1991
19. Tsukuma H, *et al*: Risk factors for hepatocellular carcinoma among patients with chronic liver disease [see comments]. N Engl J Med, 328(25):1797–1801, 1993