Non-tumoral elevation of alpha-fetoprotein (AFP) : a 10 year follow-up in two subjects

I. Timba, A.P. Geubel

Hôpital Général de Yaounde, Cameroun and Department of Hepatogastroenterology, Cliniques Universitaires St Luc, Université Catholique de Louvain, 1200 Bruxelles, Belgium.

Abstract

Elevation of serum alpha-fetoprotein (AFP) in the absence of any liver disease or malignancy, likely of genetic origin, is an uncommon observation which may be the source of diagnostic difficulties in routine clinical practice, especially in cases without available familial data. Animal studies suggest that the anomaly may be related to a mutation located in a regulatory gene different from that mapped for AFP. The transmission pattern of the defect is unknown with a strong suggestion for an autosomal dominant inheritance. We report the cases of two patients in whom a stable elevation of unknown origin of the tumoral marker for up to 10 years, has been observed in the absence of any detectable liver and/or malignancy and in whom the lack of familial data was the source of diagnostic difficulties. (Acta gastroenterol. belg., **2002**, 65, **179-181**).

Key words : alpha-fetoprotein, genetic, benign.

Introduction

Alpha-fetoprotein (AFP) is a major serum protein produced in embryo by the fetal liver and digestive tract (1). It was described for the first time in 1963 by A. Belev as a tumor marker and has been shown elevated in hepatocarcinoma and other various types of cancer (2).

An increase of the level of this protein in serum is also observed, though less frequently, in various liver diseases in which it is believed to reflect some state of liver regeneration (3), during the second quarter of pregnancy, in postnatal pediatric hereditary diseases (4-5), but also rarely and for unknown reasons, in the healthy adult. In rare cases, a genetic origin of the anomaly has been postulated or documented (6,7,8,9).

We report two cases of isolated serum alpha-fetoprotein elevation in adults without any available familial history and in whom a 10 year follow-up failed to show any evidence of liver disease or extrahepatic neoplasm.

Case reports and methods

1) Case reports

Case 1

In October 1990, an AFP elevation to 38.2 ng/ml (normal < 10 ng/ml) in combination with normal liver biochemistry was discovered incidentally in a 70 year old female. The subject was an only child. Her previous medical history included a total radical hysterectomy performed in 1986 for non-tumoral reasons, a moderate hypercholesterolemia an the removal of a benign thyroid nodule in 1987. At that time, she exhibited an excessive alcohol intake (90-100 g/day) and was smoking 20 cigarettes per day.

Her clinical examination was unremarkable. Liver function tests were all in the normal range as well as blood iron parameters and alpha-1-antitrypsin levels. Serology for hepatitis B was negative as was that for hepatitis C assessed in 1990. A moderate elevation of serum AFP was noted which persisted in the long term (table 1), and this despite alcohol discontinuation.

Radiological workup, including upper abdominal ultrasound and liver CT, showed a few renal cysts as well as two small sized simple hepatic cysts. During the following years, further examinations including gallium scintigraphy, abdominal nuclear magnetic resonance imaging and hepatic arteriography were also performed showing no significant abnormalities but the two liver cysts whose size remained unchanged. A moderate hypothyroidism was discovered which was substituted from 1995. Since then the patient has remained alcohol abstinent and asymptomatic. Yearly liver ultrasound did not showed any change. The last AFP value obtained in august 2001 was 42.6 ng/ml.

Case 2

A serum AFP elevation up to 25.3 ng/ml was observed, also incidentally in a 72 year old male during the evaluation of a hives-like reaction in 1984. Upper abdominal ultrasound and liver biochemistry were both normal as well as a complete work-up which included testis echotomography. The patient had a high blood pressure and is the eldest member of a family of two children ; his 70 year old sister has been shown to exhibit normal AFP levels in another laboratory (4,7 IU/ml ; N : < 10 IU ml).

In August 1997, a further biological examination was performed because of fatigue associated with diffuse abdominal discomfort and bloating. AFP levels was 19.1 ng/ml, serology for hepatitis B and C was negative.

Address for reprints : A.P. Geubel, Dpt of Gastroenterology, Cliniques Universitaires St Luc, 10, Avenue Hippocrate, 1200 Brussels, Belgium.

Table 1. — **Evolution of AFP levels (ng/ml) during follow-up in the two reported cases**

Case 1	10/90 38.2	06/91 42	08/94 47	02/95 42	10/98 48	08/00 39.5
Case 2	05/84 25.3	05/98 19.10	03/99 22.9	09/99 22.5	03/00 18.6	09/00 23.3

A upper GI endoscopy was unremarkable. However, duodenal biopsies showed villous atrophy. The suspicion of coeliac disease was confirmed by the positivity of both IgG anti-gliadin antibodies (1200 U. ; N < 25 U) and IgA anti-endomysium antibodies (1/40). At that time, further liver ultrasound and upper abdominal CT were performed which showed no abnormality.

Following the gluten-free diet, the clinical condition of the patient normalised and further yearly liver ultrasound remained unremarkable. Serum AFP elevation persisted during the entire follow-up period (table 1), the last value obtained in march 2001 was 23,6 ng/ml.

2) Methods

Before may 15th, 2001 AFP determination was performed using an immunoradiometric-immunoassay (IRMA ; Abbott Diagnostic division, Abbott Park, IL., USA). Thereafter, determination was performed by immuno-luminescent assay (ILMA ; Bayer Corp. East Walpole, Ma., USA).

Discussion

We have reported a long-term elevation of serum AFP level in two cases and this, in the absence of any liver disease and/or evidence of extra-hepatic malignancy. Genetic screening was only possible in the single sister of patient 2 who exhibited a normal serum level of the protein.

AFP is a major serum protein. Its structure is similar to that of albumin. It is produced by the fetal liver and, to a lesser extent, by the fetal digestive tract. At birth, serum levels decrease and in adults, detection of concentrations in the ng/ml range requires sensitive methods such as radioinummoassay (10). AFP is a marker of liver carcinoma, non-seminal germ cell tumors, stomach, pancreas, colorectal, bronchial cancer, and large sized liver metastases. It is however also elevated during the second quarter of the pregnancy, with levels of 35-75 ng/ml during weeks 16-20, particularly in the presence of neural-tube defect (11,12). A transient or permanent AFP elevation (< 500 ng/ml) may also been observed in non tumoral hepatic diseases such as acute or chronic alcohol-, drug- and virus-induced hepatitis, as in cirrhosis of various causes (13), In those cases, elevated AFP is believed to reflect inflammation and/or active regeneration (14,15,16), In acute liver necrosis its prognostic value remains however debated.

The literature reports only a few cases in whom a genetic etiology as been postulated or documented (6,7, 8). In those cases where AFP elevation was detected in various incidental circumstances, AFP levels were persistendly slightly elevated. In another more recently reported case, high serum levels of the protein varying between 200 and 800 ng/ml were documented in the proband with values varying between 637 ng/ml and 1080 ng/ml in the patient's child and two siblings (9). A single genealogical study performed in one of those patients with elevated AFP levels in four generations has been published, leading to the conclusion of a genetic origin and the suggestion of an autosomal mode of inheritance (8). Human AFP has been mapped to chromosome segment 4q112q21 (GE). Since studies performed in mouse suggest that other genes are involved in AFP gene regulation (8,17), it is tempting to make the assumption that in human with a genetic elevation of AFP, as in some mouse strains, a mutation(s) in this regulatory pathway may be the source of to a continued production of AFP.

In our cases, the absence of emerging liver disease and/or malignancy in the long-term bring strong arguments in favour of the benignity of the anomaly even if there was no available evidence for a genetic origin.

In conclusion, clinicians should be aware of the existence of rare cases with a benign elevation of serum AFP levels which may be difficult to interpret in the frame of screening for malignancy or during pregnancy. A genetic origin can only be confirmed by an etiologic evaluation and, when available, by the family history. When suspecting such an anomaly, family screening is mandatory.

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