A Case of Hereditary Persistence of \(\alpha\)-Fetoprotein: Diagnostic Usefulness of the Subfraction Profile

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\(\alpha\)-Fetoprotein is a well-established tumor marker for non-seminomatous germ cell tumors. Elevated \(\alpha\)-fetoprotein levels, however, result from a variety of clinical conditions. Hereditary persistence of \(\alpha\)-fetoprotein is a rare benign disorder in which serum \(\alpha\)-fetoprotein levels are persistently elevated, but there are no disabilities and symptoms. A 35-year-old man was diagnosed with pT1 testicular embryonal carcinoma. Post-orchiectomy \(\alpha\)-fetoprotein levels remained persistently elevated without clinical or radiographic abnormalities. His mother’s elevated \(\alpha\)-fetoprotein levels confirmed the diagnosis of hereditary persistence of \(\alpha\)-fetoprotein. Lens culinaris agglutinin-reactive \(\alpha\)-fetoprotein fractions have been reported as a useful diagnostic marker for non-seminomatous germ cell tumors; in this patient, its measurement showed high non-reactive \(\alpha\)-fetoprotein levels, which indicated the low probability of residual tumors. The present case represents the third case of hereditary persistence of \(\alpha\)-fetoprotein in Japan, and the first in which the \(\alpha\)-fetoprotein subfraction was evaluated.

Key words: HPAFP – LCA – Lens culinaris agglutinin – testicular tumor – tumor markers

INTRODUCTION

\(\alpha\)-Fetoprotein (AFP) is an integral tumor marker to treat patients with non-seminomatous germ cell tumors (NSGCTs) (1). Seventy percent of the patients with NSGCTs have elevated serum levels of AFP before treatment (2). Continued elevated serum AFP levels after orchiectomy generally indicate residual or recurrent tumor even in the absence of clinical or radiographic findings.

Elevated AFP levels, however, result from various clinical conditions such as other malignancies (3), non-neoplastic liver diseases and the hereditary persistence of AFP (HPAFP). HPAFP is a rare benign disorder and there is no need for it to be cured. We report here a case of testicular embryonal carcinoma associated with persistent elevated AFP levels, which was correctly diagnosed as HPAFP by measuring serum AFP levels in family members.

CASE REPORT

A 35-year-old man with an unremarkable medical history visited our hospital complaining of a nodule in the right testis. A solid mass 10 mm in size was palpated at the lower pole of the right testis. Initial laboratory data showed a serum AFP level of 23.1 ng/ml (normal range: 0–10 ng/ml), but no other abnormality was found from human chorionic gonadotropin, lactate dehydrogenase, liver and kidney function tests and hepatitis screening. The computed tomography (CT) and magnetic resonance imaging showed no lymph node enlargement and metastatic lesions. A right orchietomy was performed. The post-operative diagnosis was pT1 embryonal carcinoma without lymphovascular invasion. In the subsequent examination until 21 post-operative days, AFP levels had fluctuated between 22 and 25 ng/ml.

Careful evaluation for occult cancer revealed no abnormality. Lens culinaris agglutinin (LCA)-reactive fractions
showed a high non-reactive AFP (AFP-L1) ratio of 98.7% that indicated much lower probability of residual and recurrent tumors. Considering hereditary traits, his parents were screened with formal consent. The serum AFP levels of his father and mother were 6.9 and 20.6 ng/ml, respectively (Fig. 1). His mother had no hepatic disorders or hepatitis virus infection. Further close examinations including positron emission tomography/CT revealed no detectable clinical and radiographic abnormalities. At this point, we concluded that the persistent elevation of AFP was due to the HP AFP. Two cycles of adjuvant chemotherapy with bleomycin, etoposide and cisplatin were performed.

He has been free of disease for 3 years since the operation, and the AFP levels remained in the range of 19–27 ng/ml.

DISCUSSION

HP AFP is a rare autosomal dominantly inherited benign disorder in which serum AFP levels are persistently elevated but no clinical disabilities or symptoms are manifested. To the best of our knowledge, including the first descriptions by Ferguson et al. (4) in 1983, 19 cases of HP AFP have been documented in the English language literature (5). Serum AFP levels have been reported to range from 15 to 3564 ng/ml after initially planned treatments (5). The actual incidence of HP AFP remains unknown, because it is only noticed when there is a reason to test for AFP.

In the present patient, HP AFP was diagnosed correctly before prescribing inappropriate additional treatments. Although AFP has an important role in the initial diagnostic evaluation of NSGCT, the elevation of his AFP levels was thought unlikely to be related to the testicular tumor for the following reasons: (i) the elevation of AFP levels was stable before and after orchiectomy; (ii) immunohistostains were negative for AFP in the resected testicular tumor; and (iii) detailed radiographic evaluations did not show the possibility of occult malignancies. Consequently, we dealt with the remaining causes. Houwert et al. (5) reported eight cases of HP AFP patients presenting with urological disorders, four of whom were administered unnecessary treatments such as surgery and chemotherapy. Attention should therefore be paid to this benign condition to prevent misdiagnoses in those patients with elevated AFP levels.

Three specific polymorphisms in the AFP promoter gene have been pointed out as etiologic explanations for HP AFP (6). Nevertheless, neither known nor any other mutations were detected in the present patient. Although gene analyses had been previously performed in eight families, two other families revealed no mutations in the AFP promoter region. Among three families without genetic cause identified, 10 out of 12 persons showed lower elevated AFP levels of <160 ng/ml, whereas the levels of AFP were 180 ng/ml or more in all 21 persons with any identified mutation. These results, therefore, might indicate the etiologic heterogeneity of HP AFP other than point mutations at the AFP promoter region.

The AFP subfraction profile may be a good indicator for the assessment of NSGCT patients with elevated AFP levels. Total AFP is resolved into three isoforms according to the binding capacity for LCA (7). Hepatocellular carcinoma patients show a high percentage of the AFP-L3 fraction, which exhibits a strong affinity to LCA. It has been widely used for differentiating between malignancies and benign liver diseases (8). The usefulness of the AFP subfraction profile as a diagnostic marker for NSGCTs has also been reported (9,10). AFP derived from NSGCTs reportedly contains the AFP-L2 fraction (intermediate affinity) (11) in addition to the L3 fraction (10). Hence, AFP-L2 and L3 could be helpful markers in the evaluation of NSGCTs. In the present case, a very low percentage of AFP-L2 and L3 indicated no residual or recurrent tumor.

HP AFP needs to be taken into consideration in patients with unexplained persistent elevation of AFP, and its subfraction measurement might be of assistance. The present case represents the third case of HP AFP in Japan, and the first in which the AFP subfraction was evaluated.

Conflict of interest statement

None declared.

References


