

Androgen-related hepatocellular tumor of the liver associated with Fanconi's anemia

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ABSTRACT

Hepatocellular tumors are quite rare in pediatric age group. Its association with Fanconi's anemia and androgen therapy is well known but the pathogenesis is controversial. Occurrence of significant dysplasia causes great problems to differentiate it as hepatocellular adenoma or hepatocellular carcinoma. In this paper a 13 years old male case of hepatocellular tumor associated with Fanconi's anemia and androgen therapy is presented. He was given androgen and steroid therapy for 5 years and he had had hepatitis C virus infection for 3 years before the multifocal hepatic tumors were observed. Androgen therapy was withheld and surgery was performed twice. Patients taking androgenic-anabolic steroids should be carefully monitored with US and CT and tumor markers should be measured. The worrisome pathology that may occur in hepatic tumor in children particularly with androgen therapy does not necessarily predict malignant behaviour. [Turk J Cancer 2003;33(1):51-54]

KEY WORDS:

Hepatocellular tumor, Fanconi's anemia, androgen therapy

INTRODUCTION

Hepatic tumors are rare lesions in pediatric age group (1). The most common pediatric tumors of liver are hepatoblastoma, hepatocellular carcinoma, benign vascular tumors, mesenchymal hamartoma, sarcoma and adenoma in order of occurrence rate. Hepatocellular adenoma (HCA) is principally seen in young women and childbearing age with an increasing incidence since the advent of oral contraception (2). This tumor is observed in children generally with associated disorders such as Fanconi's anemia (FA), type I glycogen storage disease, combined immune-deficiency with ADA deficiency (2). If there is no abnormal hormonal or metabolic milieu, it needs great caution to diagnose a spontaneous HCA, since these neoplasms might represent well-differentiated hepatocellular carcinoma (WD-HCC) (3).

Children with Fanconi's anemia have bone marrow aplasia, characteristic somatic defects and chromosomal breaks and a predisposition to leukemia and squamous cell carcinoma. Hepatic tumors however, have not been reported in Fanconi's patients in the absence of androgen therapy or post transfusion cirrhosis (4).

In this study, a case of hepatocellular tumor in which differential diagnosis of hepatic adenoma and well-differentiated hepatocellular carcinoma was a great problem is represented.

CASE REPORT

A 13 years old male with Fanconi's anemia suffered from the disease for 5 years with prednisolone and oxymetholone therapy. He had got hepatitis C infection for 3 years. He was admitted to the hospital with vomiting, stomachache and gastrointestinal bleeding symptoms. An abdominal ultrasonography and CT showed an irregular nonhomogenous, hyper-hypoechoic mass in three foci that were 13 cm, 4.5 cm, 3 cm in greatest dimensions in right and left lobes of liver. The suspected diagnosis was hepatocellular carcinoma. He also had a horseshoe kidney. Dynamic MR, Doppler ultrasonography and scanning with endoran were not fully successful for differential diagnosis of the mass (Figure 1). There was no clue for a metastatic site. Serum α FP, which is considered the most useful marker of malignant hepatic tumors, was in normal limits in our case.

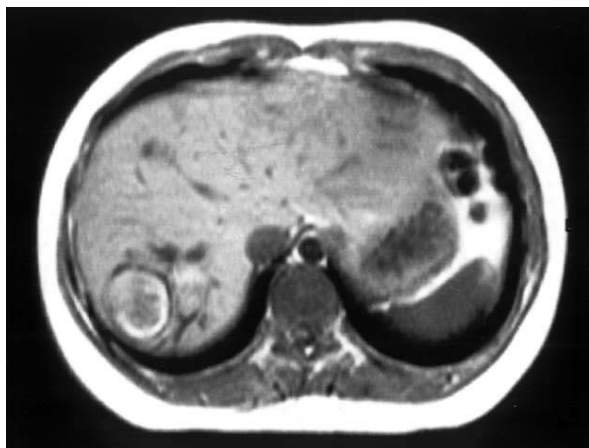


Fig 1. Large hepatic tumor during the first diagnosis (MR)

The first tru-cut biopsy from the liver was not diagnostic consisting of normal hepatic parenchyma. Needle biopsy by ultrasonographic guidelines represented the lesion but was not satisfactory for differential diagnosis of HCA or WD-HCC. Immunohistochemical detection of α FP was negative.

The final diagnosis could only be supplied by partial resection material of the mass. Tumoral masses of right lobe posterior segment (10 cm) and left lobe (7 cm) were resected. The macroscopic appearance of the partial resection material of the tumor showed a multifocal appearance. Several masses existed ranging from 1-5

cm in diameter. These masses were irregular. The cut surface was yellow or tan-coloured with haemorrhage in some areas. Thick collagen bands transverse the tumor, dividing it into cellular nodules. Tumor cells were large with abundant deeply eosinophilic cytoplasm. Tumor cells were arranged in diffuse or nodular sheets or small groups (Figure 2). Marked pleomorphism and cytological atypia were observed in some areas (Figure 3). Tissue α FP was negative. The diagnosis was androgen related hepatocellular tumor according to recent suggestions (3). Therapy of Fanconi's anemia was changed. Androgen therapy was withheld but steroid therapy was continued. After 3 months of the mass showed 30% decrease in dimensions. Second operation was planned after 6 months for the residual mass of the left lobe. Control MR at the 6th month after diagnosis showed a 4.5 cm mass at left lobe of the liver (figure 4), he underwent a second resection. The pathologic appearance was the same. The patient is well and alive since the last operation, 30 months after initial diagnosis. No chemotherapy or radiotherapy was applied.

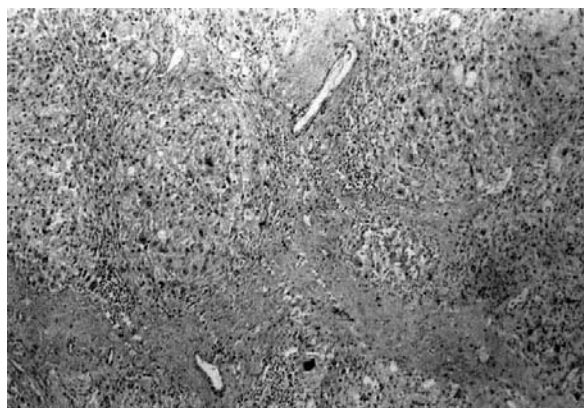


Fig 2. Tumor cells in solid, nodular sheets (H&E, x40)

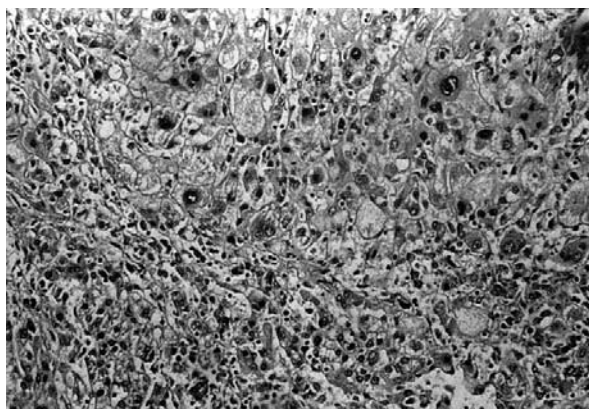


Fig 3. Cytological atypia and marked pleomorphism in tumor cells (H&E, x100)



Fig 4. Postoperative view of the lesion after 6 months of androgen cut off (MR)

DISCUSSION

HCA's are quite rare in children in whom they account for 2% to 4% of all hepatic tumors. Sex hormone imbalance, for instance usage of anabolic/androgenic steroids in the treatment of chronic anemia or hypogonadism is the most common association of HCA in children (3). Associated metabolic disorders include glycogen storage disease (most commonly type Ia) familial diabetes mellitus and Hurler's disease (3).

An association between Fanconi's anemia and hepatocellular neoplasm was first reported in 1965 as an incidental autopsy finding in a patient with advanced postnecrotic cirrhosis who had received testosterone therapy. In 1971, Bernstein et al. (5) described hepato-

cellular carcinoma complicating oxymetholone therapy of Fanconi's anemia in a non-cirrhotic patient. Both estrogens and androgens are capable of tumor progression as promoters of hepatic neoplasm, and in Fanconi's anemia, chromosome instability may serve as the substrate for enhanced oncogenesis (1).

The distinction between adenoma and carcinoma in patients with Fanconi's anemia is difficult to draw, since tumor that have cytological features associated with HCC may regress following androgen withdrawal. Androgen-related hepatocellular tumors which are typically multiple, demonstrate marked cellular pleomorphism, prominent nucleoli and extensive pseudoglandular formation, resembling HCC (3).

Occurrence of significant dysplasia in tumor cells of children with Fanconi's anemia, causes a nosologic dilemma to call the tumor hepatocellular adenoma or carcinoma. Proliferating cell nuclear antigen labelling index in lesions with Fanconi's anemia is found significantly greater than adenomas of other children (2). There is only one FA case treated with anabolic steroids in the literature defined by Bernstein et al. (5) that developed metastatic HCC. But pulmonary metastases had not been confirmed by tissue diagnosis.

What would be the role of C hepatitis infection in this patient? Has it played a role in the development of tumor? Would it cause malignant transformation? Hepatitis B virus infection is known to be associated with the development of hepatocellular carcinoma endemic or sporadic. In adult hepatocellular carcinoma, the sequence of nucleic acids of the hepatitis C virus was detected by polymerase chain reaction method in tumor tissues, but no association between hepatitis C infection and childhood HCC has been demonstrated (6).

The importance of steroid metabolism in tumorigenesis has been investigated. In an experimental study by Eagon et al. (7) it has been shown that preneoplastic stages such as hyperplasia of liver there is an elevation of both receptor activities and that the progression from hyperplasia to cancer results in suppression of oestrogen receptor expression but maintenance of androgen receptor.

Acute leukemia, hepatocellular carcinoma and squa-

mous cell carcinoma have been reported in-patients with Fanconi's anemia (8). LeBrun et al. (9) described a 9-year-old boy with Fanconi's anemia. He had been treated with oxymetholone, a synthetic androgen for 3 years. He had died of intracerebral hemorrhage and at autopsy the liver had contained several adenomas and a large fibrolamellar hepatocellular carcinoma.

They also question the malignancy of liver tumors in Fanconi's anemia patients. These tumors perhaps should be simply labelled "Hepatocellular neoplasms". This will reflect their uncertain malignant potential (3,9). There are two Fanconi's anemia patients known to have liver tumors that produced pulmonary metastasis.

This case may include malignant potential with microscopic atypia, cellular pleomorphism occurrence of C hepatitis infection. But androgen therapy as etiological factors in Fanconi's anemia, low proliferation activity, the well-documented reports about regression of these tumors with androgen withdrawal encouraged us to follow this patient after surgery without any chemotherapy.

In conclusion, patients taking androgenic-anabolic steroids should be carefully monitored with US and CT and tumor markers should be measured. The worrisome pathology that may occur in hepatic tumor in children particularly with androgen therapy does not necessarily predict malignant behaviour.

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