Eur J Pediatr (1993) 152:691–693

European Journal of
Pediatrics

Hepatic tumours during androgen therapy in Fanconi anaemia

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Received: 20 May 1992 / Accepted: January 1993

Abstract. The occurrence of liver tumours in the course of Fanconi anaemia (FA) has been well documented. We present a case, review the literature and conclude that androgen therapy would increase the risk of developing tumours, most of which appear to be benign (adenomas or peliosis) and androgen-dependent, generally decreasing in size after cessation of treatment. Survival of patients is poor, mostly because of the rapid evolution of untreated FA, rather than rupture or degeneration of the tumour. In the absence of an allogenic bone marrow transplantation, administration of haematopoietic growth factors might be effective. As a preventive measure, other types of unsubstituted androgens may be used.

Key words: Fanconi anaemia – Androgens – Hepatic tumour – Hepatic adenoma – Peliosis

Introduction

Fanconi anaemia (FA) is a rare autosomal recessive disorder (1/90000 live births) characterized by a dysmorphic syndrome and pancytopenia treated by administration of anabolic steroids. The development of liver tumours during the evolution of FA is typical, especially during androgen therapy. We present a case report and review the problems of disease management and possible aetiological hypotheses.

Case report

Our patient, born on August 25 1979, the only son of unrelated parents, was diagnosed as having FA in October 1985, based on the presence of aplastic anaemia and associated abnormalities (hexadactyly, rudimentary thumbs, thin triangular face, increased skin pigmentation, retarded growth). Numerous spontaneous chromosomal breaks in the mitoses of cultured blood cells (14/50 mitoses) confirmed the diagnosis. Androgen therapy was started in March 1986 with norethandrolone on the basis of the haematological status, and of the absence of an HLA geno-identical donor within the family. Haematological parameters improved within 1–3 months: he never required a transfusion and had no particular problems, except for deafness attributable to FA.

After 4.5 years of treatment (0.30–0.66 mg/kg per day), he developed febrile jaundice with voluminous and painful liver enlargment (9 cm below the costal margin) within few days. No other changes were observed, in particular no splenomegaly or adenopathy. Blood chemistries revealed cytolysis (levels of transaminases 15–20 times the upper limit), moderate hyperbilirubinaemia (total 46 μmol/l; direct 26 μmol/l) and an inflammatory syndrome (C-reactive protein 100 mg/l; fibrinogen 7.8 g/l). His haemoglobin level was 64 g/l, white blood cell count 2.6×10^9/l (neutrophils, 29%), and platelets were 165×10^9/l. Bone marrow was hypoplastic but without blast cells. Abdominal echography and magnetic resonance imaging showed three voluminous intrahepatic lesions, 4, 8.5 and 12 cm in size. The former two resembled adenomas, whereas the third showed signs of necrosis and liquid infiltration in the centre and appeared to be more malignant, compressing the inferior vena cava and the right branch of the subhepatic vein. Levels of α-fetoprotein, γ-decarboxyprothrombin and carcino-embryonic antigen were also normal and serological searchs for A, B, C and "nonA-nonB-nonC" hepatitis were negative. A surgical biopsy of the 8.5 cm tumour was taken, with difficulty due to heavy haemorrhage during the operation as a result of the friable nature of the tumourous liver. Pathological examination of two biopsy fragments favoured a diagnosis of adenoma (data not shown). No specific treatment was instituted despite the possible malignant character of the largest lesion. Norethandrolone treatment was stopped when jaundice occurred; no other steroid treatment was started. Sixteen months later, the lesions had regressed by more than 50%. However, the patient's haematological status deteriorated within 6 months, with profund agranulocytosis requiring frequent transfusions. A blast crisis with chromosome 7 monosomy led to infectious complications and probably to the patient's death.

Discussion

The first case of liver tumour in a patient with FA was described in 1965 [15]. In 1987, Alter [2] reviewed 25

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Abbreviations: FA = Fanconi anaemia; HCC = hepatocarcinoma

Table 1. Epidemiological aspects of hepatic lesions in FA associated with androgen therapy

Histology	Analysis of 32 patients[a]
Tumours	81%
Well-differentiated hepatoma	34%
Adenoma	32%
Malignant hepatoma	6%
Unspecified	9%
Peliosis alone	19%[b]
Sex distribution	64% male, 36% female
Average age at time of discovery of tumour	15.5 years (5.5–38 years)
Average duration of androgen therapy	5 years (0–10 years)
Cases discovered by chance	30%
Survival after discovery of hepatic lesion	50% at 1 year

[a] Our observation and 31 cases of the literature between 1965 and 1990 [1–3, 6, 7]
[b] Association of tumour and peliosis: 5%

hepatic lesions and calculated the frequency of these tumours in FA patients to be 5%; however, this is probably an underestimation since not all the cases are reported and FA patients must live long enough to develop this complication.

Most of the lesions were benign and corresponded to adenomas or peliosis (Table 1), the others being malignant: more or less well-differentiated hepatocarcinoma, angiosarcoma and cholangiosarcoma. Peliosis is characterized by cystic dilatations filled with blood corresponding to distended sinusoid capillaries [7]; mechanisms leading to its formation are unknown, and 50% of cases occur in the absence of androgen therapy [11]. Adenoma is a rare tumour which, when not in conjunction with FA, affects mostly women under oestrogen-progestogen treatment. Androgen-dependent adenomas, in both FA and non-FA cases, may have histological particularities, including nuclear atypia (occasionally large nucleoles, sometimes binucleated nuclei), well-defined acinar formation and plugs of bile. These anomalies could not be taken as an indication of malignancy, since they are also found in unaffected tissue. In addition, the major criteria of malignancy are not seen, such as capsular extrusion and vascular invasion. Levels of α-fetoprotein were always normal and were only increased in clear cases of malignant hepatoma [5]. Therefore, it is believed that most of the well-differentiated hepatocarcinomas (HCC) described in the literature were adenomas and only two cases were considered to be true HCC [16]. This point raises a problem in histological interpretation which, in order to be reliable and to allow distinction between simple adenoma and well-differentiated hepatoma, must be based on examination of excised samples or sufficiently large biopsies that contain healthy tissue.

Numerous case reports [10, 13, 17], including that presented here, describe regression after cessation of androgen treatment. This is in contrast with the evolution of adenomas seen in other liver diseases (cirrhosis, active chronic hepatitis) for which Takayama et al. [18] reported levels of malignant transformation of 22% in 1 year, of 50% in 2 years and of 80% in 3 years.

FA itself carries a very high risk of cancer, in 15%–30% of cases [2]: at least 50% are acute myeloid leukemias and 33% hepatic tumours. Among the 31 patients described in the literature diagnosed as having hepatic lesions 3 were not or only shortly (less than 3 months) exposed to androgens, including the 2 with HCC. Androgens must play a major role in this process, because many tumours regress on cessation of steroid treatment. In this regard, it would be interesting to know if hepatic tumours occur in patients belonging to one particular of the four complementation groups defined to date [17].

The principal epidemiological characteristics of these tumours are summarized in Table 1: the excess of affected males and the high frequency of cases discovered by chance should be emphasized. This tumoural complication appears later than leukaemias [2]. Median survival of these patients after discovery of the tumour is 1 year, but only 20%–25% of the deaths appear to be due to the hepatic lesion (malignancy, haemorrhagic rupture or hepatic failure). Most of the deaths reported, as in our patient, resulted from complications of the pancytopenia or from the development of leukaemia (three cases). In all case reports, androgen therapy had been interrupted and the tendency to infection increased thereafter. No author reported the use of corticoids as a replacement. Since hepatic tumours are not a contraindication for an allogenic bone marrow transplantation, its indication is imperative [16].

The mechanistic basis for the carcinogenic action of androgens is poorly understood, but some remarks are appropriate. First, an increase in the number of functional androgen receptors has been reported on HCC cells, relative to surrounding healthy tissues [12], thus enabling androgens to promote the growth of HCC cells. Second, many authors have incriminated the role of modification of the chemical structure of artificial androgens [19] because most of the products used have an α-substituted carbon 17 in common. But three cases (non FA) of hepatic tumours occurred with other androgens: metenolone [14], testosterone enanthate [4] and mesterolone [9]. Furthermore, a prospective study [14] of 254 patients with non-FA aplastic anaemia showed no difference between treatment with substituted (oxymetholone, methandienone, norethandrolone) or unsubstituted (metenolone) androgens regarding clinical or biological hepatic damage.

It is difficult to establish the benign or malignant character of the lesions, and the possibility of subsequent degeneration has to be considered. Surgical biopsy appears to be preferable both to reduce the risk of haemorrhage and to enable the distinction between adenomas and HCC; peliosis is generally diagnosed by echography. The benign character is confirmed by normal tumoural markers – γ-decarboxyprothrombin, carcino-embryonic antigen and α-fetoprotein – by the absence of metastases, particularly in the lung, and by histology of the tumour, mainly through the absence of

vascular emboli or extratumoural invasion. Regression of the tumour after cessation of androgen therapy can be followed by echography. Surgical excision, if not carried out directly, should be discussed because of the risk of spontaneous rupture, or if the mass does not regress or even increases during the follow up. There is no report of chemotherapy against malignant liver tumours in FA, but we must bear in mind that FA patients are very sensitive to irradiation and chemotherapy.

In contrast, nonintervention can be justified by the rapid fatal evolution of untreated FA, the benign nature of the majority of these liver tumours and the lack of efficient treatment for liver adenocarcinoma. Thus androgen therapy may be maintained unless the tumour becomes too large, and not to take a biopsy unless excision becomes necessary.

Another problem with FA patients is the rapid and fatal evolution caused by cessation of androgen therapy. The usefulness of haematopoietic growth factors, given when an HLA-matched bone marrow donor is not available, is under investigation: recombinant human granulocyte colony-stimulating factor or recombinant human granulocyte-macrophage colony-stimulating factor could reduce the incidence of infectious complications [8]. The mapping and cloning of some genes involved in FA [17] will help in understanding the biochemical basis of this disease and may lead to specific therapy.

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