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Recurrent hepatocellular carcinoma and non-classic adreno-genital syndrome

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Abstract. – OBJECTIVE: Hepatocellular carcinoma (HCC) is one of the most common fatal cancer in the world and androgens are among the possible etiological factors. Congenital adrenal hyperplasia (CAH) is a group of inherited diseases caused by enzyme failure in the steroid biosynthesis of the adrenal cortex, resulting in an augmented 17-hydroxyprogesterone, androstenedione and testosterone production. While the occurrence of testicular adrenal rest tumors and adrenocortical tumors in congenital adrenal hyperplasia is well described in the literature, no data on HCC occurrence are available.

CASE PRESENTATION: A 35-years-old Italian man of Caucasian origin, affected by non-classic CAH due to partial 21-hydroxylase deficiency came to observation for revaluation of his adrenal picture. Besides common hormonal and biochemical analysis, an abdomen Magnetic Resonance Imaging was performed, resulting in an 18 mm large nodular lesion between liver segments VII and VIII. Radiological reports matched with an increased serum α-fetoprotein level. A surgical removal of the lesion was performed. After that, several recurrences of the lesion, which was consequently treated by radiofrequency ablation, occurred. Every recurrence was accompanied by an increase in testosterone and steroid hormone binding globulin serum levels.

CONCLUSIONS: Our report suggests the need for screening of liver lesions in males affected by this syndrome.

Key Words:
Congenital adrenal hyperplasia, Hepatocellular carcinoma, Testosterone, SHBG, Follow-up.

Introduction

Congenital adrenal hyperplasia (CAH) is a group of inherited diseases caused by enzyme failure in the steroid biosynthesis of the adrenal cortex. There are plenty of types, numbered in increasing order of seriousness: the most common (95%) is type 3, also known as 21-hydroxylase deficit, due to the mutation of CYP21A2 gene. CAH caused by 21-hydroxylase deficit is a continuum spectrum of different disease severity, depending on enzyme residual activity, thereby depending on genotypes. If there is no residual enzyme activity, the patient is affected by a classic salt-wasting form with clinical evidence of a total cortisol and aldosterone deficiency. A residual activity of 1-2% defines the simple virilizing form where elevated androgens levels are the main issue[1]. The mildest form is the so-called non-classic form (nCAH), which is much more frequent, occurring in approximately 1 of 1,000 Caucasians and more commonly in certain ethnic groups, such as Ashkenazi Jews (1:27), Hispanics (1:53), Yugoslavs (1:62) and Italians (1:300)[2]. In nCAH enzyme activity goes from 30 to 50% and the slight decrease in aldosterone and cortisol production leads to enhanced secretion of the adrenocorticotropic hormone (ACTH) from the pituitary gland, thus stimulating biosynthesis of the adrenocortical androgens, which are independent of 21-hydroxylase, with an accumulation of 17α-hydroxyprogesterone (17OHP), androstenedione and testosterone[3]. In contrast to the salt wasting and simple virilizing forms, patients with nCAH present with mild partial cortisol insufficiency and hyperandrogenism. A delayed or wrong diagnosis may lead to infertility, oligomenorrhea, acne, hirsutism and voice problems in females, whereas males with nCAH are less studied[4].

While the occurrence of testicular adrenal rest tumors and adrenocortical tumors in the spectrum of CAH is well described in literature[5], no data on

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HCC occurrence are available, despite the role of androgens as etiological and/or progression factor in such malignancy.

Therefore, we present a peculiar case of recurrent HCC in a young adult affected by nCAH followed by a brief review of the unfrequently discovered neoplasia in nCAH.

Case Presentation

A 35-years-old Italian man of Caucasian origin, affected by adrenal hyperplasia due to partial 21-hydroxylase deficiency (nCAH), diagnosed at the age of 10 for anticipated adrenarche and micro-orchidism with positive ACTH test, came to our observation for revaluation of his adrenal picture. His sister, as well, had already been diagnosed nCAH via genetic tests. The patient had a history of moderate to severe mental retardation (total IQ less than 45 at the evaluation), mild grade gastro-esophageal reflux disease (GERD) and carbohydrate intolerance. His medication included Ursodeoxycholic acid (300 mg/day) and Esomeprazole (20 mg/day). He had not been previously treated with suppressive or replacement therapy, resulting in a chronic exposure to high testosterone levels. During the hospitalization type 2 diabetes and subclinical hypothyroidism were also diagnosed.

The patient showed an elevated 17-OH-Progesterone (P): basal 9.1 ng/ml, after ACTH 22 ng/ml (stated by electro-chemiluminescence method or ECLIA, normal range 0.2-0.8 ng/ml); testosterone levels were 15.9 ng/ml (ECLIA, normal range 2.5-8.4 ng/ml). Oral hydrocortisone (10+5 mg/day) had been prescribed.

An abdomen Magnetic Resonance Imaging (MRI) was performed for adrenal investigation, resulting in an 18 mm large nodular lesion discovered in the liver between segments VII and VIII. This new formation was difficult to characterize due to technical limitations of the MRI evaluation. Contrast Enhanced Ultrasound and Computed Tomography (Figures 1 and 2) confirmed the presence of the lesion and suggested increased arterial vascularity and a portal/parenchymal phase washout. Radiological reports matched with a slightly increased serum α-fetoprotein level (14 ng/mL, Chemiluminescent Immunoassay, normal value <9 ng/ml). Viral etiologies (HBV, HCV) were ruled out by serological investigation.

On the basis of needle biopsy assessment, which showed a hyperplastic-adenomatous high cancerous risk lesion with focal inflammatory infiltration and biliary metaplasia of hepatocytes in a non-cirrhotic liver, he underwent, in October 2014, a surgical removal of the lesion (resection of the VIII segment).

Histological findings (Figure 3) showed HCC with moderate differentiation (G1/G2). After surgery an unexpected lowering of testosterone levels (1.1 ng/ml) was detected.

Liver resection surgery was complicated by acute respiratory distress syndrome, *Pseudomonas aeruginosa* upper respiratory infection, chylous ascites, supra-vescical abscess and sepsis for which the patient was admitted in intensive care

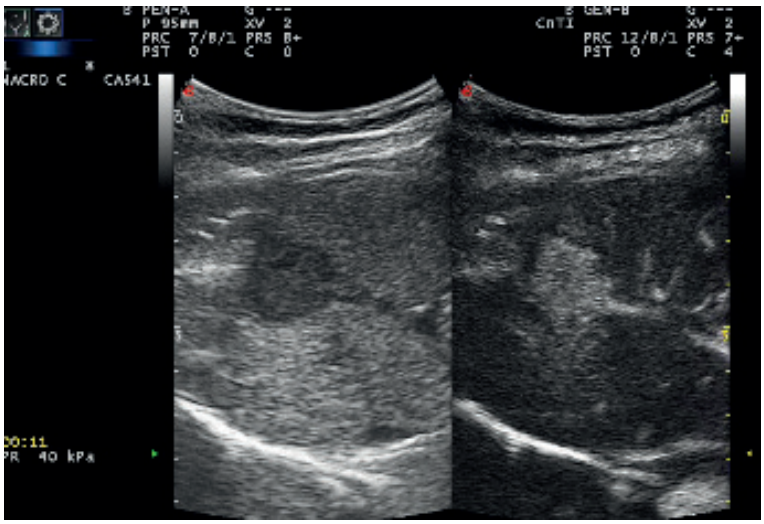

Figure 1. Ultrasound evaluation. Contrast-enhanced ultrasound image describing a nodular 18 mm lesion characterized by uniform early-phase enhancement.

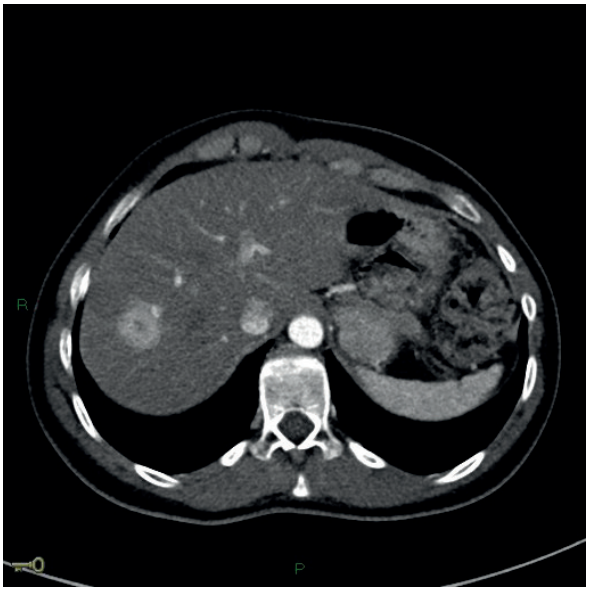

Figure 2. CT evaluation. Contrast-enhanced computed tomography image showing a nodular 18 mm lesion with increased vascularity.

unit. During the hospitalization a percutaneous endoscopic gastrostomy and non-cuffed tracheostomy tube were placed.

Six months later, on a contrast enhanced CT of the abdomen, a new lesion 5 mm large hypervascularized in arterial phase, recurred in VIII segment. However, due to the inability of the patient to tolerate MRI and to aspecific findings of contrast enhanced ultrasound, no intervention was performed; short term follow-up with serum α-fetoprotein monitoring and liver ultrasound was planned.

Given the elevation of α-fetoprotein, testosterone and steroid hormone binding globulin (SHBG) serum level and nodular lesion growth on liver ultrasound, in October 2015, a contrast enhanced abdomen CT was performed. The lesion of the VIII segment was 15 mm large and showed a dynamic behavior (hypervascularized in arterial phase with washout in portal/late phases) suggestive of HCC recurrence.

Radiofrequency thermal ablation was performed with success; α-fetoprotein, testosterone and SHBG serum level decreased significantly.

Two other recurrences, July 2016 (8 mm nodule of the VII segment) and May 2017 (13 mm nodule of the VII segment) were detected by imaging methods during the subsequent strict follow up and were treated with the same technique. The third recurrence (December 2017), detected with contrast enhanced CT, was characterized by a new HCC nodule 30 mm large of the II segment with portal infiltration, recurrent HCC lesions in the VII-VIII segments (overall diameter 30mm), and faded pulmonary nodules in the right basal area probably due to HCC metastasis. Sorafenib (orally active multikinase inhibitor approved for the treatment of advanced HCC) 400 mg/day was administered and then suspended after twelve weeks for serious skin rash occurrence. Trans-catheter arterial chemoembolization (TACE) was then performed with palliative intent. A new bilobar progression of the neoplasm was detected. In February 2018 HCC recurred. No other intervention on the neoplasms was performed, only symptomatic therapies were continued until death occurred one month later.

Every recurrence was accompanied by elevation of testosterone, but also SHBG serum levels, as described in Table I; therefore, we hypothesized a facilitating effect of chronic androgen elevation, otherwise a possible production of SHBG by tumor itself.

Tumors detected in nCAH

A higher prevalence of benign tumors has been described over the ages especially in salt-wasting and simple virilizing CAH, sometimes in nCAH either, mostly of adrenal and testicular origin[5-8]. Some authors have speculated about increased risk for malignancy in CAH[9,10], even if cancer mortality has not been shown to be increased in comparison to general population[11].

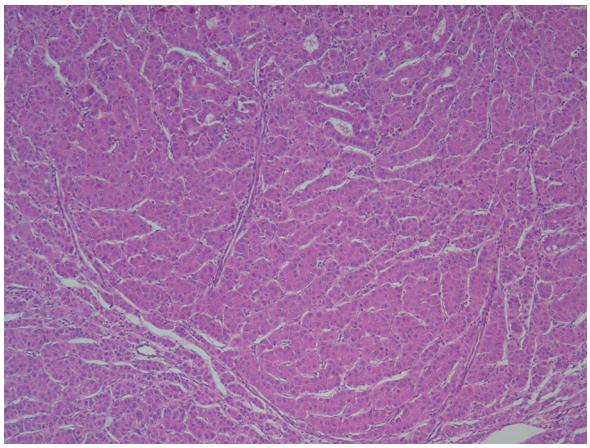

Figure 3. Histological findings (x10). Hyperplastic-adenomatous lesion with focal inflammatory infiltration and biliary metaplasia of hepatocytes.

Table I. Hormonal and α-fetoprotein levels throughout the follow-up.

	Testosterone (ng/ml)	SHBG (nmol/L)	Free testosterone (ng/mL)	17-OH-progesterone (ng/mL)	α-fetoprotein (ng/mL)
Normal range	2.5-8.4	15.0-65.0	0.046-0.181	0.3-2.5	<9
June 2014 (pre-surgery)	15.8	102.1	0.201	9.1	14
December 2014 (after surgery)	11.1	47.2	0.223	4.7	7
June 2015	15.1	125.6	0.141	11.5	17
October 2015	9.7	94.0	0.197	8.7	14
November 2015 (After first RFA)	11.0	42.7	0.018	4.7	7
July 2016 (Before second RFA)	15.1	125.6	0.149	11.5	15
August 2017 (after third RFA)	8.0	154.0	0.056	10.1	11

TARTs

Testicular adrenal rest tumors (TARTs) are benign testicular tumors commonly found in CAH for an overall estimated prevalence of 40%[12]. Their prevalence increases according to age, especially in puberty[13], and according to the severity of the disease, as they are mostly diagnosed in severely affected CAH patients[14]. They are considered the main cause of infertility in CAH men, mainly attributed to obstruction given by the mass, oligospermia, and decreased testicular testosterone production[15]. Due to their central location in the rete testis, TARTs can be detected by testicular palpation only when bigger than 2 cm. The gold standard examination for diagnosis is MRI and ultrasound[12]. On ultrasound they usually appear hypoechoic, while on MRI hyperintense on T1-weighted images and hypointense on T1-weighted ones[16].

CAH patients with this kind of neoplasia usually have higher serum levels of androstenedione, 21-deoxycortisol and 17-OHP in spermatic vein blood than in peripheral one[17], suggesting the steroid production of cancer cells. Moreover, CAH patients with TARTs compared to CAH patients without them have higher serum levels of androstenedione, 11β-hydroxytestosterone, 11-ketotestosterone, androsterone and allopregnanolone[18]. The discrimination between TARTs and Leydig cell tumors (LCTs) may be challenging since they share common morphological features. However, discrimination is crucial because TARTs are benign tumors only to be removed when causing severe pain, while LCTs are always removed with a malignancy rate of 10%. TARTs are typical of CAH, whereas LCT description in this disease is uncommon[19-22]. Moreover, TARTs are often (77%) bilateral, whereas bilateralization is present only in 10% of LCTs; finally, from a histopathological point of view, Reinke's crystals are sometimes present in LCTs, never in TARTs[12].

While data on TARTs in salt-wasting and simple virilizing forms of CAH are several and well-known, the prevalence in nCAH is still debated. Six studies[13,23-27] including patient with nCAH (37 patients, gathering them together), did not evidence TARTs on ultrasound. On the other hand, in literature five cases of TARTs in the mildest form of CAH are known and reported as "incidental findings"[5,28,29].

The first choice in TARTs treatment is represented by corticosteroid treatment, in particular dexamethasone and prednisone, aiming to suppress ACTH, thus granting a reduction of tumor size and, according to some reports, improving testicular function[30]. The use of mitotane and human chorionic gonadotropin combined with Follicular Stimulating Hormone (FSH) has been reported to be successful to restore fertility in two different works[31,32]. Testis-sparing surgery is indicated only in presence of severe pain, as it does not restore fertility[33]. No preventive therapy is currently available[12].

Adrenal Tumors

Adrenal tumors formation, detected with a frequency of 11-82% according to CT/MRI ex-

aminations[4], may be the consequence of a long exposure to elevated ACTH levels[4,7]. The great majority of them are myelolipomas[8,34]. The size of the tumor correlated positively with 17OHP and pregnanetriol levels[8,35]. Some studies have evaluated in patients with uni- or bilateral adenomas the frequency of undiagnosed CAH and CYP21A2 mutations on only one allele (CAH carriers), which were respectively the 6% and the 16% of the totality[36-38]. In contrast, Barzon et al[39] has detected only a 0.5% of the patients with adrenal incidentalomas to be affected by CAH. In literature there are several reports of nCAH diagnoses as the result of the work-up of these tumors[37,40-43]. Even though adrenocortical cancer is rare in CAH, there are occasional case reports both in CAH[9,44], sometimes associated with myelolipomas[45] or comprised in an adrenal collision tumor[46], and in nCAH[47,48].

Other Reports

In literature some other singular cases of other tumors in nCAH have been described, such as LCTs[21,22]. No data on HCC in nCAH are reported.

Discussion

Hepatocellular carcinoma (HCC) is one of the most common fatal cancers in the world. A possible role, among etiologic factors, is attributed to androgens. Hepatocytes exhibit androgen receptors and a cell proliferation stimulus is exerted by testosterone or dihydro-testosterone. This association is present even after adjustment for the presence of HBV, HCV, cirrhosis, alcohol consumption and smoke vat[49,50].

The prevalence of HCC in CAH is not described in literature; moreover, males affected by late-onset CAH are not investigated with the same accuracy of females. On the other hand, male sex is accounted as a risk factor for HCC[49,51]. This kind of neoplasia has a higher prevalence and a worse clinical course in males[52]. It is an old statement that hepatic tumors in male rodents are increased in strains with chronic hyperandrogenism[53]. The role of testosterone is still debated even if androgen receptors (AR) are present in hepatocytes, both in nucleus and in cytoplasm; their expression and activation are augmented both in tumor and in surrounding tissue of patients with HCC[54]. Anti-androgens block receptor-mediated tumor growth in rodents[55]. Finally, a low number of CAG repeats of AR gene has been associated with greater cancer risk[56]. Testosterone plasma levels, SHBG and insulin-like growth factor (IGF)-1 have been considered prognostic factors in HCC, however the etiologic role remains unclear[57].

In our patient the lesion was incidentally discovered during morphological follow-up of adrenal glands. The clinical course was particularly severe, requiring repeated radiofrequency thermal ablation procedures.

Every recurrence was accompanied by elevation of testosterone, SHBG serum levels either, as above described; therefore, we hypothesized a facilitating effect of chronic androgen elevation, but also a possible production of SHBG by tumor itself. However, even when SHBG decreased after surgery, a chronic hypertestosteronemia was sustained by the adrenal secretion.

The limitations consist in the lack of immunohistochemical and gene expression analysis. We could not establish if SHBG derived from tumoral secretions; therefore, we could not discriminate between the two etiological hypotheses previously stated.

Conclusions

This report suggests the need for screening of liver lesions in males affected by this syndrome; the role of testosterone in inducing or facilitating the neoplasia and the possible involvement of SHBG secretion remain to be established.

Conflict of Interests

The Authors declare that they have no conflict of interests.

Authors' contribution

EV, CB and AM are major contributors in writing the manuscript. SR, LR, FRP and MP are contributors in writing the manuscript. AM, SR, EV and CB have followed the patient during the evolution of the disease. GM has performed radiological examinations. FMV has performed histological evaluations. LR, FRP and MP have performed ultrasound evaluations and managed the anti-neoplastic treatment. All the authors read and approved the final manuscript.

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