Hepatocellular adenomas associated with anabolic androgenic steroid abuse in bodybuilders: a report of two cases and a review of the literature

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CASE REPORT 1

In this first study we report a 35 year old male bodybuilder who has been taking AAS at high doses over the last 15 years. During this period a number of AAS were self administered in cycles of 8 weeks with a suspension period of 2 weeks between cycles. The following AAS were the most frequently consumed by the patient: (a) oral: stanozolol and oxymetholone; and (b) parenteral: nandrolone decanoate, testosterone enanthate, and methenolone enanthate.

The doses and the frequency of self administration were, approximately, 400 mg daily for oral AAS and 600 mg twice or three times a week for parenteral AAS, varying in each cycle.

The patient was completely asymptomatic, with no signs of jaundice, when he was included in an experimental follow up examination programme for bodybuilders. In general terms, there was no relevant previous history. Neither daily intake of ethanol or smoking were reported. In the clinical examination performed shortly after admission to the program, our patient showed severe hepatomegaly. Laboratory evaluation revealed slight damage of liver function (ALT: 75 IU/l; AST: 53 IU/l; alkaline phosphatase: 403 IU/l; GGT: 60 IU/l; total bilirubin: 1.6 mg/ml; direct bilirubin: 0.42 mg/dl) and muscular damage (CPK: 298 IU/l). Coagulation tests were entirely normal, as were serum levels of alfa-fetoprotein (AFP). Hepatitis virus markers, including hepatitis B and C, were negative. Serum levels of sex hypophyseal hormones (FSH and LH) were evaluated but were not detectable.

Abdominal ultrasound (US) showed two large hypeerecogenic lesions in the liver, one in the left lobe (6 cm in size) and another in the right (12 cm in size). The largest lesion showed a heterogeneous pattern, thus indicating the existence of haemorrhage areas in the tumour. In colour Doppler ultrasonography blood flow signals could only be detected at the peripheral areas of both tumours. These results are concordant with adenomas at first diagnosis.

Cytology was performed by fine needle puncture-aspiration (FPA) of the nodules. The cytological samples did not reveal any malignancy. Subsequently, the patient was subjected to magnetic resonance imaging (MRI). The MRI study confirmed the diagnosis of liver cell adenomas (fig 2A and B). T1 weighted MRI showed a heterogeneous signal in both lesions, although this heterogeneity was more intense in the lesion of the right lobe. In T2 weighted MRI showed a heterogeneous pattern, thus indicating the existence of haemorrhages in the tumour. In colour Doppler ultrasonography blood flow signals could only be detected at the peripheral areas of both tumours. These results are concordant with adenomas at first diagnosis.

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Anabólicos androginos (AAS) son usados ilegalmente a altas dosis por bodybuilders. El consumo de estos fármacos está asociado con efectos adversos graves, incluyendo adenomas hepáticos y adenocarcinomas. Se reportaron dos casos diferentes de adultos con músculos y tejido adiposo que desarrollaron adenomas hepáticos secundarios a AAS. El primer caso fue asintomático pero tenía dos lesiones hepáticas que se detectaron por ultrasonidos después del cese de la adrenalina. El segundo paciente fue admitido en nuestro hospital con insuficiencia renal aguda. Se realizaron exámenes serológicos de hepatitis y virus de la hepatitis B y C, que resultaron negativos. Se examinaron primero las lesiones hepáticas por ultrasonido, que mostraron un patrón heterogéneo, lo que indicaba la existencia de áreas de hemorragia. En el paciente, las lesiones hepáticas mostraron una tasa de regresión después de la administración de AAS. Los casos presentados aquí son raros pero pueden ser sugerentes de la tendencia a regresar después de la retirada de AAS. Los casos presentados aquí son raros pero pueden ser sugerentes de la tendencia a regresar después de la retirada de AAS.

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**Abbreviations:** AAS, anabolic androgenic steroids; AFP, alfa-fetoproteína; FPA, punta de aguja; MRI, resonancia magnética; US, ecografía.
the considerable size of the lesions, it was not possible to establish any therapeutic guidelines, with the exception of absolute prohibition on self-administering AAS and the inclusion of this patient in a liver transplantation program. The patient has been followed biannually by means of US and analytical studies.

The patient was subjected to clinical, radiological, and analytical tests 1 year after diagnosis. Biochemical values showed a persistent slight alteration in liver function. AFP serum levels stayed normal, while US studies demonstrated that the lesions had remained unaltered and of the same size as the year before the persistent slight alteration. To confirm the absence of any malignancy, a biopsy under ecographic control was performed. The histological findings showed neither portal tract in the tumor nor capsule formation around it. The nuclei of the tumour cells showed mild atypia and a low degree of anisonucleosis. These histopathological results confirmed again that the lesions were non-malignant tumours.

At present, 4 years after the diagnosis and subsequent to further ecographic examinations, to our surprise, there has been a slight decrease in the size of the tumours (of about 1–2 cm in the tumour in the left lobe and 3–4 cm in the tumour in the right lobe) (not shown). Liver function has also clearly improved. Serum levels of transaminases have returned to normal, as have the other serum markers of liver function. As in previous examinations, coagulation tests and serum levels of AFP were absolutely normal. On the other hand, the serum levels of sex hypophyseal hormones (FSH and LH) were evaluated and found to be normal, thus suggesting that the withdrawal of AAS may have induced the total recovery of the hypothalamic–hypophyseal axis. However, the patient continues in the above mentioned liver transplantation program and undergoes periodic examination because of the enormous size and the potential malignant transformation of the liver lesions.

**CASE REPORT 2**

We report another patient, a 23 year old male bodybuilder, with diverse severe symptoms and signs affecting different organs and systems due to misuse of various AAS at high doses. The patient had commenced treatment with AAS (and diuretics) 6 months before the appearance of the symptoms and had undertaken stringent diets for increasing muscle mass prior to competition. AAS were administered in cycles of 8 weeks, twice or three times a week, varying in each cycle, with a suspension period of 2 weeks between cycles. Each week the bodybuilder self administered the following AAS: (a) oral: stanozolol and oxymetholone; and (b) parenteral: nandrolone decanoate, testosterone phenylpropionate, and boldenone.

His nutrition also went through cycles. During the first 3 months he followed a hypercaloric and hyperproteinic diet to build up muscle mass. There then followed a phase of reduced caloric intake to lessen subcutaneous fat. He also severely restricted Na⁺ and water intake and self administered a diuretic, torasemide, to attain better muscle contour definition by reducing extracellular and subcutaneous tissue volume.

The patient began to show symptoms after 6 months of treatment with AAS and 1 month of treatment with diuretics and a restrictive diet. He then stopped training and drug self administration and was admitted to the emergency service of our hospital in a confused state. The patient displayed asthenia and anorexia of 1 month duration. Analytical data reflected acute renal failure (urea: 304 mg/100 ml; creatinin: 10.2 mg/100 ml), muscular damage (myoglobinuria; CPK: 5499 IU/l; ALT: 178 IU/l; AST: 130 IU/l; LDH: 716 IU/l), metabolic alkalosis (pH: 7.62; Pco₂: 66.1 mm Hg; Po₂: 80.6 mm Hg; HCO₃⁻: 77.8 mEq/l), hypokalaemia (K⁺: 2.12 mEq/l), and hypernatraemia (Na⁺: 147 mEq/l). Neither a daily ethanol intake or smoking were reported. It is well established that AAS induce fluid retention with hypernatraemia. Excess Na⁺ in the blood produces an increasing rate of K⁺ and H⁺ excretion, inducing metabolic alkalosis and hypokalaemia and, consistently, a decrease in the respiratory frequency with compensatory respiratory acidosis. The marked hypokalaemia suffered by the patient could be explained by the fact that this bodybuilder did not maintain an adequate Na⁺, K⁺ and water intake over the training periods, and, furthermore, self administered a loop diuretic. This marked hypokalaemia favoured muscle damage and rhabdomyolysis. Furthermore, the high doses of self administered AAS presumably promoted aggression and other changes in attitude that could explain the excess training
despite muscle weakness due to hypokalaemia. This situation resulted in multiple ruptures of muscle fibres (increasing serum values of CPK, AST, ALT, LDH, and elevation of blood levels of myoglobin and myoglobinuria). The increase in myoglobin renal excretion, with subsequent cylinder formation in the nephron or direct toxicity to tubular cells, led to acute renal failure.

At physical examination, abdomen, heart, lung, and the neurological system showed normal functioning. Bradypyschia, confusion, and asthenia were the most obvious symptoms. The patient was admitted to the nephrology unit for haemodialysis to treat renal failure. US performed shortly after admission showed mild hepatomegaly, with a very close hyperecogenic nodules in segment IV, concordant with adenomas (fig 3). FPA of these nodules did not reveal any malignancy.

Coagulation tests were entirely normal, as were AFP serum levels. Serum levels of sex hypophysal hormones (FSH and LH) were evaluated but were not detected. After diagnosis, the patient underwent three haemodialysis sessions and was encouraged to rest as much as possible, with absolute prohibition on self administering AAS. The biochemical values of the patient returned to normal 20 days later, except for the hormonal serum values. Once the acute renal failure, asthenia, and confusion had resolved, he was discharged from hospital.

US studies performed 1 year later showed a decrease in the size of the hyperecogenic hepatic nodules (not shown) and biochemical analytical values were close to normal.

**DISCUSSION**

Hepatic adenomas (HA) are uncommon benign neoplasms, usually occurring in young women who take oral contraceptives. In recent times anabolic androgenic steroids (AAS) have been proved to be involved in the development of HA. Although more than 750 cases of oral contraceptive induced HA have been reported, apparently androgen induced HA are relatively rare. However, the possibility that oral AAS such as stanozolol can induce liver cell proliferation must be taken into account.2

HA are not malignant tumours, but surgical intervention may be required if sudden massive bleeding or liver failure occurs; rupture of HA with haemoperitoneum can be a life threatening complication.8–11 HA are hypervascular tumours containing multiple sinusoids of capillaries with thin walls in which the pressure is exclusively arterial. The connective tissue support is poor and, therefore, bleeding tends to spread diffusely throughout the entire tumour.10 A non-surgical approach should be considered for androgen induced HA, given that some tumours have regressed after AAS administration was stopped.7–9, 12

One of the problems that HA present is differentiation between HA and hepatocellular carcinomas (HCC). In fact, radiological findings in patient with HA are often similar to those in patients with HCC.2, 12–14 In those cases in which clinical, radiological, and histological distinctions between HA and HCC are difficult to determine, surgical resection, if possible, may be recommended.2 In our patients, histopathological studies of liver specimens obtained by FPA and biopsy allowed us to establish the diagnosis of HA.

Another problem with HA is their potential for malignant transformation, although this point is still controversial. Rapid progression of tumours and tumour obstruction of the intrahepatic portal veins, demonstrated by US, CT, or MRI studies, could indicate the possibility of malignant transformation. For this reason, a careful follow up of HA patients by means of US studies every 6 months is absolutely necessary.2, 8, 14–16

Several reasons make it difficult to establish a general strategy of treatment of hepatocellular adenomas: the risk of haemorrhage, the technical difficulties encountered in tumour excision, and the uncertain risk of malignant transformation. These factors determine the prognosis of the disease.9–12 In a number of cases, other therapies, such as ethanol injection therapy or radiofrequency ablation, should also be evaluated.8 Thus, young men with HA should undergo tumour resection, even when there is no liver failure, rupture, or malignant transformation. However, in the cases here reported hepatic resection has not been performed because of the size and number of the tumours. Furthermore, the fact that following the last test there was an evident decrease in the size of the lesions in both cases opens the possibility that in future years the first patient may be operated on and his lesions resected and in second patient the lesions may regress spontaneously. The clinical evolution of these cases indicates that withdrawal of AAS self administration is the main, and possibly the only, therapeutic tool necessary in cases of early diagnosis of the tumour. In contrast, in evolved cases, with late diagnosis, surgical treatment will probably be necessary.

**CONCLUSIONS**

Sportsmen, especially bodybuilders, taking anabolic androgenic steroids over a long period should be considered a group at risk of developing hepatic sex hormone related tumours, and should therefore be monitored annually with US examination. Periodic US studies seem to be an adequate screening procedure to detect the development of space occupying lesions. Up to now, when one of these tumours was diagnosed, or even suspected, in an asymptomatic patient, immediate surgical excision was recommended. The risk of intraperitoneal haemorrhage, which can be fatal, justifies more aggressive initial management. Nevertheless, a non-surgical approach for tumours associated with androgens has been suggested because of the regression of tumours after AAS administration was stopped. In any case, after a diagnosis of liver tumours the administration of AAS should cease and the patient should be carefully monitored, preferably twice a year, with biochemical analyses of liver function, AFP serum levels, and US studies.

![Figure 3](image-url)

**Figure 3** Abdominal ultrasound showing hyperecogenic nodules close together in the liver of the second patient.
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What is already known on this topic

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Informed consent was obtained from the two patients described in this report.

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What this study adds

The cases reported by us reinforce the importance of withdrawing anabolic-androgenic steroids. In our experience, the first therapeutic approach to androgen induced hepatic adenomas should be, if possible, the absolute prohibition of taking anabolic-androgenic steroids. In some cases, where the size of the tumours is not very large, this therapeutic approach could be sufficient.

REFERENCES