Multiple hepatocellular adenomas associated with long-term administration of androgenic steroids for aplastic anemia: a case report and literature review

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Abstract
Introduction: Anabolic steroids are widely administered to patients with aplastic anemia (AA) and are associated with numerous medical complications. To assist with future diagnoses, we report about a young boy with multiple hepatocellular adenomas (HAs) induced by long-term use of anabolic androgenic steroids (AAS) for AA and present a related literature review.

Patient concern: A 15-year-old boy who was diagnosed with AA in 2011 had been treated with stanozolol (6 mg per day) and ciclosporin A (120–150 mg per day) for almost 4 years. He presented with epigastric pain and fever, and abdominal computed tomography showed a lesion of heterogeneous density measuring 13.5 x 13.0 x 8.0 cm in the left hepatic lobe, which was initially misdiagnosed as a liver abscess.

Diagnosis: The patient went into hemorrhagic shock twice after invasive manipulation that aimed at diagnosis and was finally diagnosed with HA using fine needle aspiration.

Interventions: The patient discontinued AAS and only reserved ciclosporin A for AA treatment.

Outcomes: Follow-up abdominal computed tomography performed 4 years after AAS discontinuation showed obvious regression of the hepatic lesions.

Conclusion: It is of great importance for hematologists to completely understand that the long-term use of AAS may cause HA, which carries a great risk of hemorrhage and malignant transformation.

Abbreviations: γ-GT = γ-glutamyltranspeptidase, AA = aplastic anemia, AAS = anabolic androgenic steroids, AFP = α-fetoprotein, ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, CUS = contrast-enhanced ultrasound, CT = computed tomography, FNA = fine needle aspiration, FNH = focal nodular hyperplasia, HA = hepatocellular adenomas, HAE = hereditary angioedema, HGB = hemoglobin, MRI = magnetic resonance imaging, NE# = neutrophil absolute value, PLT = platelet, TAE = transarterial embolization, US = ultrasound, WBC = white blood cell.

Keywords: anabolic androgenic steroid, aplastic anemia, hepatocellular adenoma ;

1. Introduction
Anabolic androgenic steroids (AAS) are widely used by bodybuilders to achieve a rapid increase in muscle mass and by aplastic anemia (AA) patients to stimulate hematopoiesis. A growing number of reports suggest that the abuse of AAS is associated with serious adverse effects. Several liver disorders have been reported to be related to AAS administration, namely cholestatic jaundice, peliosis hepatitis, hepatocellular adenoma (HA), and hepatocellular carcinoma.[1] HA is an uncommon benign epithelial liver tumor with high risk of malignant transformation, spontaneous hemorrhage, and rupture.[2-4] As a result, early detection is important in order to avoid these associated life-threatening conditions. Here, we report a case of AAS-induced HA who suffered hemorrhagic shock because of an invasive diagnostic operation. Our aim is to share our lessons with the wider medical field and highlight the diagnosis and treatment of AAS-induced HA.

2. Case presentation
A 15-year-old boy presented to the hepatic surgery department of our hospital with abdominal pain, accompanied by fever
results indicating CD34(+), CK7(−), GPC-3(−), and β-catenin (+), finally confirming the diagnosis as HA. These multiple HAs, which were distributed diffusely in the liver, might have been induced by the long-term administration of AAS. Therefore, we recommended cessation of stanozolol consumption to the patient, and to check the hepatic lesions every 6 months. The abdomen symptoms never returned, and the hepatic lesions gradually regressed according to ultrasound (US) examinations. After discontinuation of AAS for 4 years, a final CT scan showed a low density lesion measuring 3.0 × 2.0 cm in the left hepatic lobe, which had obviously regressed (Fig. 1C).

3. Discussion

3.1. Clinical features of HA

HAs are typically solitary lesions (70%–80%) that range in size from a few millimeters to thirty centimeters, while AAS-induced HAs appear to predispose multiple lesions.[5] There is usually no fibrous capsule, and as a result, hemorrhage from an adenoma can freely extend into the liver and even into the peritoneal cavity.[6] The presence of abdominal pain, a history of extended AAS use, the subcapsular location, and an adenoma size ≥ 3.5 mm are all features associated with an increased risk of intra-abdominal bleeding.[7] As for the physical examination of HA, an abdominal lump can be identified in up to 30% of patients, while hepatomegaly is present in approximately 25%. Jaundice has also been described during presentation and presumably reflects compression of the intrahepatic bile ducts by an enlarging mass.[8,9]

In this case, the patient presented with epigastric pain and fever, while physical examination revealed obvious hepatomegaly and mild jaundice. During the diagnostic process of this case, we did not fully realize the hemorrhage risk of the tumor, resulting in the patient experiencing hemorrhagic shock twice; as these events were life-threatening, we must draw attention to this condition to raise the awareness of other hematologists.

3.2. Association between AAS and HA

In recent years, AAS have been proven to be involved in the development of HAs for the treatment of AA, hereditary angioedema (HAE), and muscle mass development in bodybuilding and transgender individuals.[10–16] A recent study enrolled 182 individuals who used AAS for ≥ 6 months and found a broad
Table 1

Summarized features of previous case reports.

| Type           | Gender and age (years) | AAS                                                                 | Duration of intake | Maximum diameter | Therapy | Single or multiple | Prognosis | Reference |
|----------------|------------------------|----------------------------------------------------------------------|--------------------|------------------|---------|--------------------|-----------|-----------|
| HAE            | Female, 69             | danazol                                                             | 20 years           | Not mentioned    | Stop AAS | Not written        | NO change in tumor size, 2 years later, this patient died from a stroke | Bork et al [14] |
| HAE            | Female, 29             | danazol                                                             | 13 years           | 11cm             | Stop AAS | Multiple           | Disappeared within 26 months | Bork K et al [14] |
| HAE AA         | Male, 39               | danazol                                                             | 16 years           | 5 cm             | Stop AAS | Single             | Disappeared after 18 months | Bork et al [14] |
|                | Female, 20             | oxymetholone                                                        | 6 years            | 5.5 × 4.8 cm     | Stop AAS | Multiple           | 2 years later, no change in the lesions | Naka et al [10] |
| HAE            | Male, 45               | danazol                                                             | 17 years           | 14 cm            | Stop AAS surgery | Single | Not mentioned | A year after surgery, no recurrence was observed | Bork et al [13] |
| Endome-triosis | Female, 37             | danazol                                                             | 14 years           | 6 cm             | Stop AAS surgery | Multiple | Not mentioned | Not mentioned | Julia Bartley et al [15] |
| Body-builder   | Male, 35               | Stanozolol Oxymetholone Nandrolone decanoate Testosterone enanthate Methenolone enanthate Stanozolol Oxymetholone Nandrolone decanoate Testosterone phenylpropionate Boldenone | 15 years           | Left lobe (6 cm) and right (12 cm) | Stop AAS Plan to liver Transplantation | Multiple | 1 year later showed a decrease in the size of the HA | Socas et al [16] (2005) |
| Body-builder   | Male, 23               | Stanozolol Oxymetholone Nandrolone decanoate Testosterone enanthate Methenolone enanthate Stanozolol Oxymetholone Nandrolone decanoate Testosterone phenylpropionate Boldenone | 6 months           | Not mentioned    | Stop AAS | Not mentioned | Not mentioned | Socas et al [16] (2005) |
| Body-builder   | Male, 27               | Androstenedione                                                     | 5 years            | 10.6 cm × 10.6 cm | Left lateral hepatic segment-ectomy | Stop AAS | Multiple | 3 months later, the HA appeared 40% smaller, after 42 months, he presented with tumor enlarge-ment, and intraperitoneal hemorrhage due to abuse AAS | Nicole et al [18] |
| Body-builder   | Male, 28               | Androstenedione                                                     | 6 years            | 10.1 × 8.1 × 5.6 cm | Surgery | Single | No recurrence was observed after six months | Pais-Costa et al [11] |
| Gender disorder| Female, 32             | Testosterone enanthate                                              | 12 years           | 2.8 cm           | Surgery radifre-quency ablation | Multiple | No recurrence was observed after 22 months | Kato et al [12] |

spectrum of liver injuries in this cohort, including hepatotoxicity (46/182) and HA (1/182). [17] Although AAS-induced HAs are relatively rare, the possibility that oral AAS can induce liver cell proliferation must be taken into consideration. We summarized 11 recently published cases of AAS-induced HAs in Table 1. The median age of these patients was 32 years old (range: 20–69), with a male/female ratio of 1.2:1 (6/5). Because many young men are body-builders, this group in particular is susceptible to AAS-induced HA. The median time from AAS intake to HA onset was 13 years (range: 0.5–20); and for that AA patient the time duration is 6 years which is similar with our case. Most of the AAS-induced HAs were multiple lesions, and the diameter of these lesions was usually greater than 5 cm.

The possibility of AAS-induced HA cannot be ruled out in our case for the following reasons. Several studies have reported stanozolol as a trigger of HA, and this patient had a 4-year history of exposure to stanozolol before the onset of HA. The clinical characteristics of this patient were consistent with those detailed in the literature; he was an adolescent male who was susceptible to developing AAS-induced HAs, and the multiple lesions seen in his liver are common indicators of AAS-induced HA. Most importantly, the lesions were significantly regressed after AAS withdrawal.

3.3. Diagnosis of HA

Since biochemical test abnormalities are rare in HA, multiple imaging modalities are of great importance for diagnosis, including US, CT, and magnetic resonance imaging (MRI) of the abdomen. HA is a vascular tumor with a predominantly arterial supply in classic cases. Expected findings consist of well-vascularized and well-defined solid lesions that are predominantly in an arterial phase on CT or MRI. As seen in our case, the lesions may be dyshomogeneous, especially if hemorrhage, necrosis, or fibrosis is present. [5,19]

Dynamic MRI with a hepatocyte-specific contrast agent, such as gadobenate dimeglumine, is the best modality for diagnosing HAs. The tumor can have a clearly defined central margin with nearly parallel vessels entering from the periphery, giving the appearance of a spoked wheel. [10] The sensitivity and specificity of MRI for HA may be as high as 88% to 100%. [21] Compared with conventional MRI, three-phase hepatobiliary MRI with delayed images has a specificity of 100% and a high sensitivity, allowing for the accurate diagnosis of HA; it is particularly valuable for HA lesions smaller than 3 cm. [22]

Contrast-enhanced ultrasound (CEUS) is a rising imaging technique that is increasingly used to diagnose liver lesions, as it is important for differentiating between HA and focal nodular hyperplasia (FNH). [23] Additionally, different molecular subtypes of HA have particular B-mode echogenicity contrast-enhanced imaging appearances, and so can be complement approaches to MRI. [24]

Percutaneous liver biopsy or FNA are usually not utilized for diagnosis because HA has a tendency to bleed following biopsy, and because the amount of tissue obtained using these methods is frequently insufficient for establishing a diagnosis. [25,26] In the
present case, FNA was an important procedure for confirming the HA diagnosis, but also resulted in intra-abdominal bleeding and hemorrhagic shock. Therefore, we learned that multiple HAs can be seen in AA patients who use AAS over an extended period, and FNA should not be recommended for diagnosis as life-threatening complications may occur.

3.4. Treatment and prognosis of HA

Treatment of HA mainly depends on symptoms, size, number of lesions, location, and risks of hemorrhage and malignant transformation, and include cessation of associated drugs, surgical resection, transarterial embolization (TAE), thermal ablation, and liver transplantation.

Conservative management may be preferred if the HA is small (<5 cm) and associated with oral AAS. In case of AAS-induced HA, discontinuation of AAS may regress the mass and thereby potentially prevent unnecessary hepatic surgery. Martijn et al. stated that 98% of HAs follow this trend, and a conservative approach could lead to HA regression below 50 mm. Moreover, a study of 180 patients diagnosed with HA >5 cm found that 81 patients (45%) treated with conservative therapy reached the clinical regression endpoint of <5 cm after a median of 34 months. In the cases summarized in Table 1, HAs either remain stable or show obvious regression after AAS cessation. In our case, the patient was diagnosed with AAS-induced HA and his left hepatic lobe also regressed from 13.5 cm to 3 cm after cessation of AAS for 4 years.

TAE is considered as the first choice in the management of hemodynamically stable patients with bleeding HA. In the elective setting, TAE has also been performed as an alternative to surgical intervention. In a systematic review of 851 patients with HA, 151 patients (17.7%) underwent TAE with a reported tumor regression rate of 75%. Complete tumor disappearance was observed in 10% of patients and surgery was avoided in 45% of patients. Thermal ablation is a common minimally invasive alternative to surgery which has been recently reported as a treatment method for HA. While current studies have only involved a limited number of patients, ablative methods have typically demonstrated efficacy for small HAs (<5 cm).

However, even after the discontinuation of AAS, growth, rupture, and malignant transformation have all been documented. Therefore, HAs that do not resolve after cessation of AAS should also be considered for surgical resection. One controversial issue in the surgical management of HA is the timing of resection after cessation of AAS therapy. Liver transplantation should be reserved for patients for whom surgical resection is not possible due to tumor size/location and for those with adenomatosis.

Moreover, male gender, tumor size, and AAS-induced HA are known risk factors for malignant transformation among patients with HA. Although the hepatic lesions of our patient were regressed obviously after AAS cessation, there is still a high risk of malignant transformation; therefore, a careful follow up of our patient by imaging methods and AFP every 6 months is necessary for continued management.

4. Conclusion

AA patients, especially those taking AAS over an extended period, should be considered at risk of developing HA. Multiple imaging modalities are considered to be the most important methods for diagnosis, while FNA should be used with caution as life-threatening bleeding complications may occur. If HA is diagnosed, or even suspected, the use of AAS should be discontinued as soon as possible and the appropriate treatment strategy should be carefully selected according to the individual’s condition. Because of the high risk for malignant transformation, patients should also be monitored carefully with biochemical analyses of liver function, AFP serum levels, and US studies.

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Author contributions

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