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Case report

Sudden unexpected death in a female fitness athlete, with a possible connection to the use of anabolic androgenic steroids (AAS) and ephedrine

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ABSTRACT

The use of anabolic androgenic steroids (AAS) has been associated with different adverse effects, some of which potentially lethal. Most users of AAS are male, but the prevalence of such use appears to be increasing in females. Here we present a sudden unexpected death in a female fitness athlete with a possible connection to use of doping agents.

1. Introduction

The use of anabolic androgenic steroids (AAS) has spread from athletes and body builders to adolescents and adults who use these compounds for aesthetic reasons [1]. The life-time prevalence of anabolic androgenic steroid (AAS) use among male adolescents in Western countries typically ranges from 1 to 5% [2]. In a recently published critical review on the prevalence of AAS use among women, it was concluded that AAS use among Western society teenage girls probably is rather limited, with a life-time prevalence of approximately 0.1% [3]. Still, according to the Anti-doping Hot-Line[1] the frequency of telephone calls from women reporting that they have used AAS has increased drastically over the last 2 years, suggesting that the prevalence of AAS use among young adult females is increasing.

The most frequently reported physical side effects that are unique to female AAS users are increased facial hair, deepening of the voice, clitoral enlargement, and menstrual cycle disturbances [4–9]. Studies also have identified side effects in women that are similar to those experienced by males, such as increased aggressiveness, increased libido, acne, and the loss of scalp hair [8,9].

When it comes to reports concerning possible lethal cardiac complications from the use of AAS, these are almost entirely confined to male users, since, as far as we know, only on such a case has been reported earlier [10]. This fact seems consistent with the notion that the use of AAS is not widely spread among females. However, since AAS use among women does exist, it is reasonable to expect that lethal complications from their use should occur, as in males, provided that such complications exist. Here, we present a report of a female death with a possible connection to the advanced use of AAS.

2. Case study

This 29-year-old woman was found naked in a prone position on the floor beside her bed, with a pillow partly under her body. She had been a successful fitness athlete and had won a major national fitness competition 3 days prior to being found dead. As a teenager, she had been apprehended by the police on several occasions for disorderly conduct while drunk, but there had been no indications of any alcohol problems or other illicit substance abuse later in life, or any known physical or psychiatric disease. Later in life, she was known to police for illicit trading with doping agents and for prostitution (illegal in Sweden).

In her apartment, a diary was found in which she had written a number of entries describing feelings of meaninglessness, but there was no explicit mention of suicidal intent. There also was a sheet of paper on which she had logged her use of AAS during the period from September 3 to May 15 of the year of her death. According to this log, she had used nine different AAS, in various combinations, during this period. In her kitchen, there were three

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[1] www.dopingjouren.se/page.asp?page=kvinnaaas.

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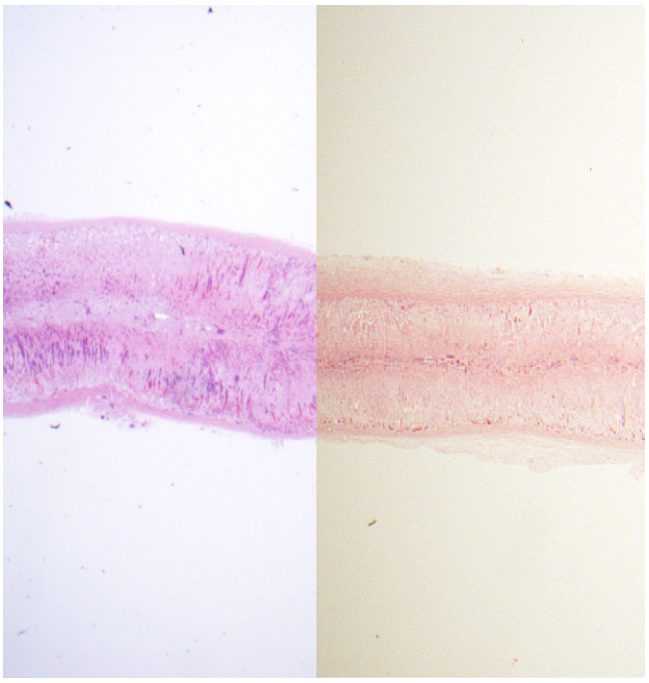

Fig. 1. Adrenal cortex hypotrophy. Normal adrenal from 32-year-old female who died from acute cardiac event for comparison (left). Heamatoxyline–eosine staine at 1× magnification.

unmarked glass jars containing five different kinds of pill, as well as three-tablet packages of clenbuterol. The unknown pills were analyzed and found to be ephedrine, tadalafil, metandienon, mestanolon, and stanozolol.

At post-mortem examination, the only external signs of trauma were a few minor facial abrasions of nonspecific character. No petechia was evident on the conjunctiva or elsewhere. She had conspicuously well-developed skeletal musculature and a strikingly low amount of subcutaneous fat. She was 172 cm tall and weighed 76 kg, for a body mass index (BMI) of 25.7. Her breasts had silicone implants. Other findings were acne-like scarring on her face, striae on the outer and upper aspects of her thighs, clitoral enlargement, and small, seemingly atrophied major labia, which were interpreted as having resulted from a general reduction in subcutaneous fat.

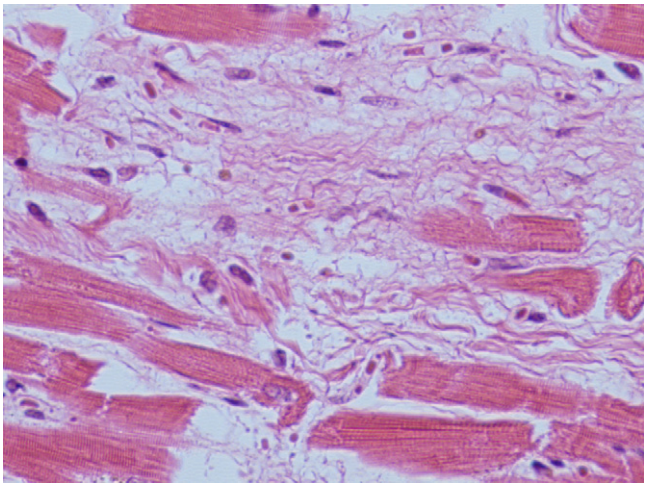

Fig. 2. Area with replacement fibrosis. From inferior part left cardiac ventricle. Heamatoxyline–eosine staine at 40× magnification.

On internal examination, there were no findings to suggest mechanical trauma or asphyxiation. The temple muscles were conspicuously well developed. The adrenals were small and thin. Microscopically, the adrenals showed diminished thickness of both the cortex and the medulla, whereas the capsula propria appeared somewhat increased in thickness (Fig. 1). The uterus was slightly

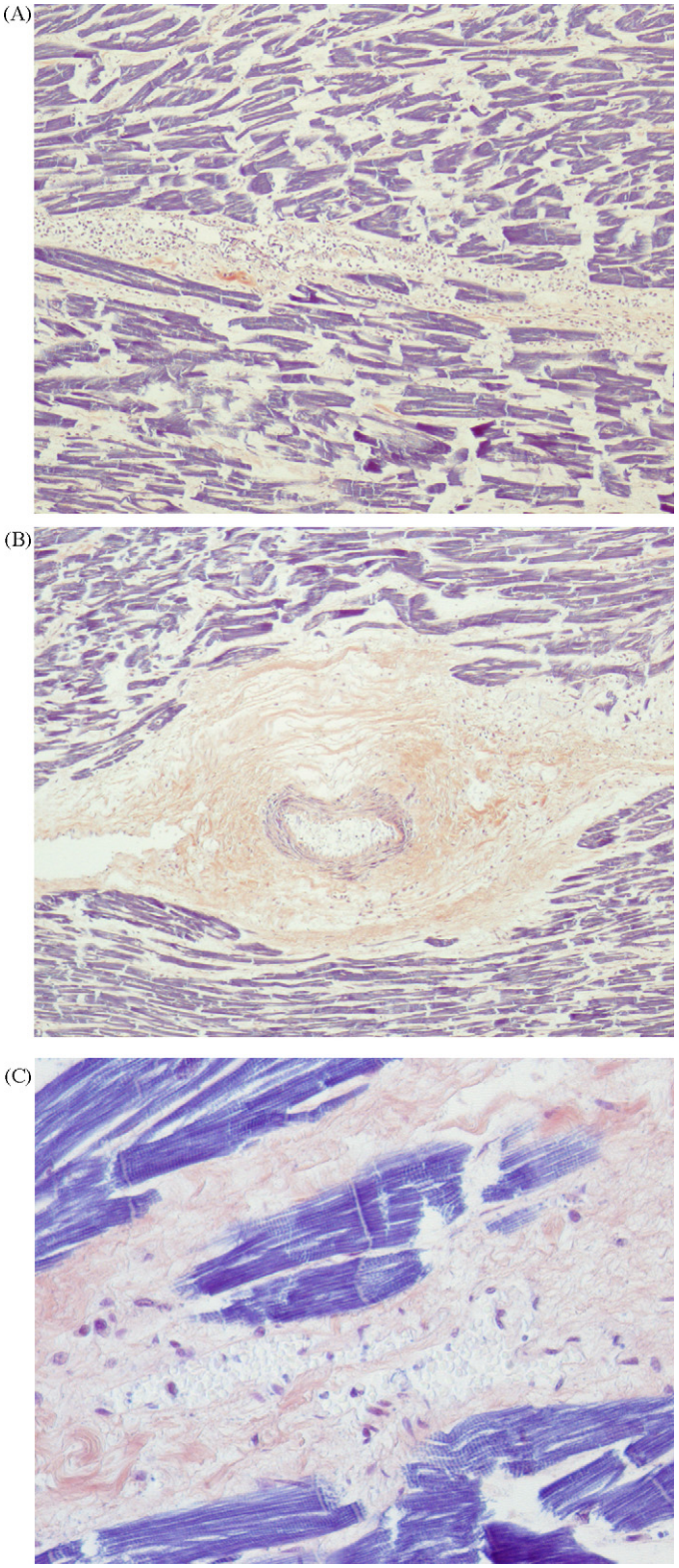

Fig. 3. Perivascluar lymphocytic infiltrates in samples from the left cardiac ventricle. PTAH staining at 10× (A and B) and 40× (C) magnification.

larger and the ovaries were slightly smaller than usual. The larger internal organs were abnormally heavy (liver: 2298 g; kidneys together: 394 g; lungs together: 1500 g) and congested. The heart was normally sized (331 g) and normally shaped, and the coronary arteries were patent, only having one isolated flat area of fatty thickening measuring approximately 0.5 cm × 0.3 cm in the proximal part of the left anterior descending (LAD) coronary artery. Samples from the heart ($n = 4$, all from the left ventricle) showed a few small foci of granulation tissue, which was interpreted as evidence of earlier, minimal myocardial necroses (Fig. 2). There also was lymphocytic infiltration around several middle-sized and small intramural vessels (Fig. 3). The lungs were congested, and examination of samples from all lung lobes revealed multiple areas with erythrocyte-containing alveoli (Fig. 4). The trachea and the larger bronchi contained moderate amounts of bloodstained froth. The liver exhibited no macroscopic changes, apart from congestion. Microscopically, the liver tissue demonstrated changes typical of early decomposition, but no obvious pathological changes.

Toxicological analyses revealed 0.4 μg ephedrine and 0.1 μg norephedrine per g blood, as well as the presence of three different AAS in the urine: 31.4 ng/ml of testosterone (reference value for females 2–3); 29.3 ng/ml of OH-stanozolol; 16.5 ng/ml of 16β-OH-stanozolol; and 2109 ng/ml of boldenon; all expressed as nanograms per ml urine. The testosterone to epitestosterone ratio was 28.3–1 (in males, a ratio exceeding 6:1 and in females a ratio > 4:1 is interpreted as highly indicative of exogenous testosterone administration). Screening for alcohol, other pharmaceuticals (see [11] for a detailed description of screening) and illicit drugs (amphetamines, opiates, cocaine metabolites, THC, MDMA-analogues) was negative in femoral blood (alcohol and pharmaceuticals) and urine (illicit drugs (immunological screening)).

Corpus vitreum analysis did not suggest any significant electrolyte disturbances or hyperglycemia ($K^+ = 9.1$, $Na^+ = 133$, $Cl^- = 113$, glucose = 0.0 and lactate = 15.2; all expressed as mmol/l). The K^+ value corresponded well with the estimated time since death, estimated on the basis of the post-mortem examination and supported by several pieces of circumstantial data; hence, it was not interpreted as an indication of hyper-potassaemia.

The most plausible cause of death was judged to be sudden cardiac arrhythmia, possibly related to the combination of (1) an otherwise unspecified inflammatory process in the heart and (2) the acute influence of AAS and ephedrine.

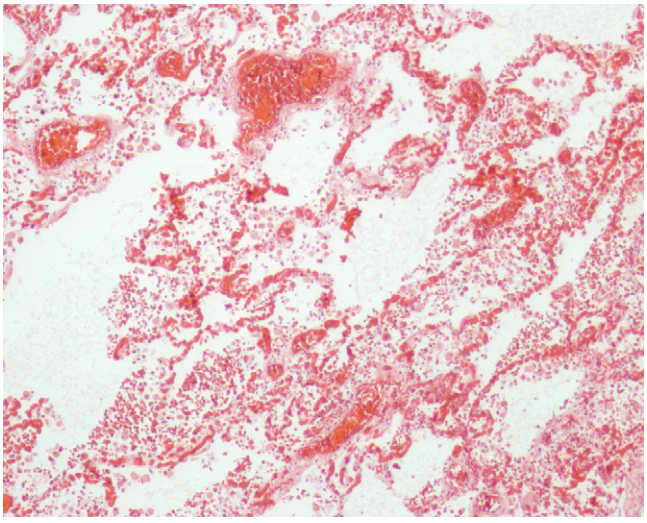

Fig. 4. Area with extravasated erythrocytes in congested lung. Heamatoxyline–eosine stain in 10× magnification.

3. Discussion

The suggested cause of death in this young woman – sudden cardiac arrhythmia possibly related to a combination of an otherwise unspecified inflammatory process in the heart and the acute influence of AAS and ephedrine – was based on the elimination of other obvious causes of death.

This assumed cause of death gains a degree of theoretical support from the fact that both AAS [12–18] and ephedra [19,20] compounds have been associated with acute myocardial infarction. Coronary vasospasm has been suggested as the underlying mechanism for ischaemia and myocardial infarction with both these drug groups [12,19]. Furthermore, both AAS [21] and ephedra [19] compounds have been associated with an increased risk of arrhythmia, possibly related to mechanisms other than acute ischaemia; e.g., by causing dysfunction in the autonomic regulation of heart rate. In this context, it is interesting to note that Phillis et al. have demonstrated that the AAS, nandrolone, significantly elevates the heart rate response to high-dose cocaine, without changing heart morphology in the rat [22]. Thus, although all above-mentioned associations derives from case reports and not controlled clinical human or animal studies, thus making causation impossible to claim, it appears reasonable to assume that an interaction between AAS and ephedrine may have been of importance in the presumed sudden cardiac death in the present case.

Although both the foci of replacement fibrosis and the perivascular inflammatory changes were rather moderate, and probably not severe enough to cause arrhythmia by themselves, both fibrosis and myocardial inflammation are known risk factors for arrhythmia [23,24]. Thus, these alterations could have constituted a possible 'morphological substrate' for a lethal arrhythmia that, in turn, was triggered by the combined actions of AAS and ephedrine.

As is usually true with case studies based on autopsy data, verifying long-term exposure to different drugs is difficult. In this particular case, there was a detailed log documenting the regular intake of AAS over the last several months preceding death. However, the long-term intake of other drugs, like ephedrine, remains unclear. For this reason, it is impossible to claim that the pathological heart changes were exclusively due to AAS intake. Considering that ephedrine is both an α- and β-adrenergic agonist that enhances the release of catecholamines, and that focal myocardial necrosis has been described as typical of catecholamine myocytotoxicity [25], the use of ephedrine should be considered to have been as potentially important in causing this woman's heart changes as the AAS she consumed. In this context, it should be kept in mind that several studies have identified an association between the use of AAS and ephedra products [26–37]. In fact, the use of AAS has been associated with the use of a wide range of illicit drugs and psychoactive pharmaceuticals [38–44]. Thus, the cardiac changes described here could well be explained by former use of other drugs, for instance cocain, which is known to have a potential of causing micro-infarctions [45]. Not only psychoactive substances, but also various pharmaceuticals intended to counteract the different side effects of AAS often are consumed by AAS users. In particular, the possibility that a presumed arrhythmia has been triggered by disturbed electrolyte balance from the uncontrolled use of diuretics should be kept in mind, when examining body builders or fitness athletes who have died suddenly and unexpectedly [46]. In the present case, the corpus vitreum electrolyte analysis did not indicate any significant disturbances of electrolyte balance. However, this test merely reflects current electrolyte status; and, given that diuretics often are used with body building or immediately prior to fitness contests to increase muscle definition, it cannot be entirely ruled

out that recent use of diuretics played a role in this woman's death. Unfortunately, diuretics are not routinely included in toxicological screening, and such data are not available for this patient.

As discussed above use of other drugs than AAS may be of importance for some of the cardiac changes. However, there is also a possibility that the perivascular lymphocyte infiltration – and perhaps also the foci of replacement fibrosis – were related to viral myocarditis. Unfortunately, no measures, such as serology or DNA sequencing, were taken to examine this possibility further. Another limitation is that the heart tissue sampling procedure was limited to only four samples from the left ventricle. Thus the cardiac conduction system was not examined.

Unlike the well-established AAS-related findings of external examinations (e.g., acne, acne-related scarring, clitoral enlargement, and a low amount of subcutaneous fat), the finding of adrenal atrophy has, to our knowledge, not been reported previously. Considering that it is well known that AAS disturbs hypothalamic-pituitary function [47], finding adrenal atrophy is not surprising. Adrenocorticotropic hormone (ACTH) induces the concomitant secretion of glucocorticoids and the endogenous anabolic androgenic steroid dehydroepiandrosterone (DHEA) from the adrenal cortex [38], and is down-regulated by means of negative feedback from cortisol. Since many types of AAS bind readily to the GR [48,49], it could be that decreased levels of ACTH, resulting from negative feedback from high levels of circulating synthetic AAS, were at least partly responsible for the atrophy of this woman's adrenal cortex.

Irrespective of the underlying mechanism of adrenal atrophy, one should consider this alteration as a possible, alternative cause of death; i.e. by causing an Addisonian crisis. In this case, however, neither the circumstances nor the analysis of the corpus vitreum supported this conjecture. In any case, we believe that adrenal atrophy, in the absence of some other obvious explanation, should be regarded as a possible indicator of long-term AAS use, for which reason we encourage careful examination, including microscopic morphometry, of the adrenals when examining cases of sudden unexpected death among athletes.

4. Conclusion

The present case report illustrates that the misuse of doping agents and related substances may be an underestimated risk factor for sudden, unexpected death, and particularly underestimated in females. For this reason, we believe that there is need both for increased surveillance and for research regarding the adverse effects of doping agents, including their possible role in lethal poly-drug misuse.

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