Case Report

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ARDS, Diffuse Alveolar Hemorrhage and Pericardial Effusion due to Anabolic-Androgenic Steroids Consumption: Legal and Ethical Policy in Medical Education

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INTRODUCTION

Image and performance enhancement drugs (IPEDs) contain an extended variety of substances that are taken to

Anabolic-androgenic steroids (AAS) are one of the ingredients of herbal and dietary supplements that are popular among sports trainers. AAS abuse predisposes everyone to several complications. Reviews of the literature on AAS users have shown mainly skin, renal, and hepatic complications. In this case report, we presented a case with simultaneous complications, including diffuse alveolar hemorrhage (DAH), acute respiratory distress syndrome (ARDS), pericardial effusion, gastrointestinal bleeding (GIB), and acute kidney injury (AKI). Given the potential for lethal complications and the consequences of ethical, civil, and criminal law, it seems that specific policies will be considered for the use of bodybuilding drugs. It is also suggested that this approach be added as a new part of the medical curriculum. Also, ARDS and DAH are unreported side effects in other studies, which is suggested to be considered by specialists.

Key words: Anabolic-Androgenic Steroids; Adverse Drug Reaction; Complications

change shape and function. IPEDs involve human growth hormones (HGH), Melanotan II, anabolic steroids, estrogen control, post-cycle, and fat loss drugs (1). Anabolic androgens steroids (AAS) are increasingly used to enlarge muscle or lose body weight. A study in England and Wales showed that the number of people aged 16 to 59 years taking this drug throughout their lives developed from 194,000 in 2005 to 271,000 in 2015 (2).

Also, more than three million young people over 13 years old from North America have experienced using AAS, and one-third of them were dependent on AAS (3). In addition, AAS dependency has been reported as a public health concern compared to type 1 diabetes mellitus and HIV infection (4, 5). AAS are usually associated with remarkable side effects, including sudden death, chronic damage to vital organs, myocardial infarction, atrial fibrillation, and affecting kidney function (6). Other side effects might be increased appetite, gastrointestinal dysfunction, acne, libido change, impotency, hirsutism, symptoms of cardiac disease, premature masculinization or feminization in teenagers, atrophic testis, infertility, and gynecomastia (5). However, simultaneous side effects such as pericardial effusion, acute respiratory distress syndrome (ARDS), and diffuse alveolar hemorrhage (DAH), have not been reported.

Acute kidney Injury (AKI) can be a common complication of abusing AAS and vitamin or mineral supplements. An allergic reaction may occur following their use, which causes interstitial nephritis and leads to AKI (4, 7). AKI is regularly associated with systemic malfunctions consisting of volume overload, electrolyte and acid-base imbalances, nutritional and gastrointestinal disorders, anemia and bleeding diatheses, and an increased risk of infection (8). Moreover, AAS abusers may face pericardial effusion (9). Many cases of DAH originated via capillarity caused by systemic autoimmune disorders, but in some cases, DAH is a consequence of coagulopathy, transplantation, toxic inhalation, or some drugs (10). The occurrence of these complications at the same time is very rare and has not been reported. In this study, we reported complications of AAS (G-fast pills) and compared them

with other case reports in the literature from 1990 to 2019. Data sources were PubMed Central (PMC), PubMed, Embase, Google Scholar, DOAJ, Medline, Web of Science, Psych Info UpToDate, Cochrane Library, and CINAHL without language restriction.

CASE SUMMARIES

A 26-year-old man was admitted to the emergency ward on November 21, 2019. He reported that he had experienced hematemesis, epigastric pain (which was not diffuse), low appetite, nausea, dizziness, and activity-related dyspnea one week before admission. On the first day of hospitalization, the patient excreted melena several times. Dyspnea was accompanied by a nonproductive cough. Physical examination revealed diminished lung sounds in bases and increased blood pressure (BP=175/105 mmHg), and an electrocardiogram (ECG) was taken. He was taking G-fast pills (one type of AAS) to increase muscle mass and strength for three consecutive days. The patient reported only eating nine capsules in three days. His previous medical history was alopecia universalis from three years ago.

Laboratory test results on admission were as follows: BUN: 180 mg/dl, serum creatinine (Cr): 12.4 mg/dl, sodium: 142 mEq/L, potassium: 4 mEq/L, calcium: 7.7 mEq/L, PT: 13, INR: 1, PTT: 45, AST: 24, ALT: 11, Albumin: 3.9 g/L, LDH: 702 U/L, CPK: 208 U/L, and CK-MB: 40 U/L. Arterial blood gases showed pH: 7.30, PCO₂: 28.7 mmHg, PO₂: 55.9 mmHg, BE: -12.6 mmol/L, HCO₃-: 13.8 mmol/L, and O₂ saturation: 87.4%. Urinary analysis showed proteinuria and glucose and no hematuria. Urine culture was negative. In stool examination, WBC, CBC, and a few yeasts were seen, and ova, cysts, and trophozoites were not found. The decision was made to fix the Foley catheter and NG tube to monitor intake and output. He also received 3-5 liters of O2 with a nasal cannula. Trinitroglycerin (TNG) drip was administered to control high blood pressure (BP=175/105 mmHg). Emergency

hemodialysis for 2 hours was performed due to high serum creatinine (12.4), and 1-unit packed cells were transfused during the procedure (Table 1).

Following the aggravation of the symptoms, he was transferred to the ICU. Physicians' orders were IV Lasix (40 mg), IV pantoprazole (40 mg), and IV ondansetron (4 mg). Antihypertensive drugs were also ordered: PO prazosin (1 mg), PO carvedilol (3.125 mg), and TNG (5-10 μ g/min).

On the second day of hospitalization, the patient was awake and complained of weakness and lethargy. There was no hematemesis, but he excreted melena several times; the blood pressure was 130/80 mmHg, and a lung CT scan was performed on him. Gradually, during the second day, the patient's level of consciousness decreased, and following respiratory distress, he underwent intubation and mechanical ventilation. Due to fluid overload, hemodialysis was prescribed for the second time.

Para-clinical tests included echocardiography, endoscopy, bronchoscopy, ultrasound imaging, spiral chest CT scan, and electrocardiography. Echocardiography showed trivial pericardial effusion, ejection friction of 40%, mild mitral regurgitation, aorta insufficiency, and mild tricuspid regurgitation. Fiber optic bronchoscopy revealed massive hemoptysis in bases. Also, sporadic erythema in the duodenum was observable in endoscopy results.

ECG upon admission was sinus rhythm (100 beats/min) and normal axis, but after a week converted to sinus tachycardia (120 beats/min), inverted T, and upsloping ST depression in II, aVF, V5, and V6, and 2 mm ST-segment elevation of V2-V4 (Figure 1). In the beginning, bilateral alveolar hemorrhage was about 100 cc, which reached 300-500 cc after a few days (Figure 2). In chest images, the ARDS trend was evident (Figure 3). During the hospitalization, after accurate patient assessments, a hemorrhage diagnosis in the alveoli was made. Specimen analysis of alveolar hemorrhage showed some clusters of bronchial tissue with enlargement nuclei (hemosiderin macrophage: 2%, polymorphonuclear neutrophils (PMNs):

90%, and mononuclear cells: 8%). The patient did not respond to painful stimuli. High fever and hemoptysis were other symptoms. Kidney and urinary tract ultrasonography demonstrated decreased parenchymal thickness and increased parenchymal echo patterns, and after tracking the serum creatinine level during hospitalization, chronic kidney disease was suggested.

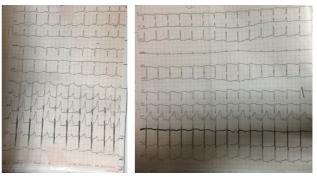


Figure 1. Electrocardiogram (ECG) upon admission and after a week



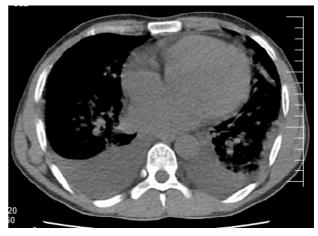


Figure 2. Bilateral alveolar hemorrhage in CT-Scan

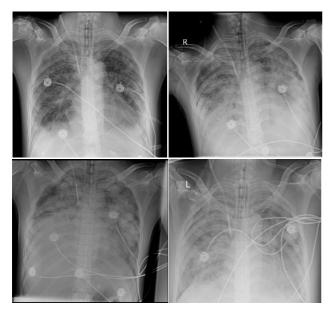


Figure 3. ARDS trend in Chest X Ray

The patient underwent plasmapheresis and hemodialysis again and also received methylprednisolone pulse therapy. The immunology tests showed normal

Table 1. Clinical and laboratory data of patient

results (pANCA: 0.4/C0.6, and FANA and DsDNA were negative). The pathology test results with specimen consisted of peripheral blood smear and bone marrow aspiration, and biopsy revealed severe leukopenia, hypochromic red blood cells, anisopoikilocytosis, decreased platelets, and existence of some schistocytes. Megaloblastic changes in the erythroid series and shifts to the left of the myeloid series were seen. Also, megakaryocytes increased in number with normal lobulation in bone marrow aspiration and hypolobulated forms in bone marrow biopsy.

With increasing alveolar hemorrhage, sepsis and septic shock occurred and hypotension (systolic blood pressure was 50 mmHg) was its consequence. The patient still had a high fever and decreased level of consciousness. After the decrease in blood pressure and heart rate, norepinephrine (20 µg/min) was prescribed during resuscitation and he finally died after 11 days of hospitalization.

	Admission	First day	Second day	Days 3 to 9	10 th day	11 th day
Vital signs	T:36.7	T:36.5	T:38.5	Min T:36.5	T:38.1	T:38.3
	RR:18	RR:17	RR:17	Max T: 38.5	RR:17	RR:15
	PR:102	PR:90	PR:95	Min RR:16	PR:95	PR:110
	BP:175/105 mmHg	BP:135/75	BP:160/110 mmHg	Max RR:18	BP:140/90 mmHg	BP:170/120 mmHg
		mmHg		Min PR:80		
				Max PR:105		
				Min BP: 105/50 mmHg		
				Max BP: 163/110 mmHg		
	-Hematemesis	-Dyspnea	-Weakness	-High fever	Aggravation of:	Unsuccessful CPR
	-Dyspnea	-Melena	-Lethargy	-Hemoptysis	-Respiratory	
Signs & symptoms		-Nonproductive	-Melena	-Decreased response	Distress	
		cough	-Decreased level of	to painful stimuli	-Decrease level of	
		-Diminished lung	consciousness	-Respiratory distress	consciousness	
		sounds	-Respiratory distress		-Fever	
			-Fluid overload			
Significant	WBC (×109)= 3.7	WBC (×109)= 7.6	WBC (×10 ⁹)= 8.9	Min WBC (×109)= 0.6	WBC (×109)= 0.4	WBC (×109)= 0.2
Laboratory tests	Platelet (×109)= 146	Platelet (×109)=	Platelet (×109)= 116	Max WBC (×109)= 14.8	Platelet (×109)= 60	Platelet (×109)= 52
	SCr(mg/dl)= 12.2	117	SCr(mg/dl)= 7.1	Min Platelet (×109)= 57	SCr(mg/dl)= 6.9	SCr(mg/dl)= 6.3
		SCr(mg/dl)= 8.1		Max Platelet (×109)= 113		
				Min SCr(mg/dl)= 4.6		
				Max SCr(mg/dl)= 9.5		

DISCUSSION

In this study, we reported a case with lethal complications due to AAS consumption. Universally, there is a burgeoning about the growing physical and psychological side effects of AAS consumption (2). Case reports of AAS users have reported more skin (e.g., acne, and balding) and renal and hepatic complications (Table 2). However, in the original studies, some serious consequences, including cardiovascular, hepatic, or renal dysfunction (physical) and mood disorders or aggression (psychological) have been reported (4, 11-13). Similar to original studies, we observed lethal complications of ARDS, DAH, pericardial effusion, gastrointestinal bleeding (GIB), and AKI in this patient.

Various side effects among male users have been reported; however, data regarding AAS side effects in female athletes are limited (Table 2). Female AAS consumers use lower doses and fewer AAS than male consumers (14). Several recorded complications of AAS use among female athletes are hirsutism, alopecia, heightening of the sound, clitoromegaly, menstrual disorders, and aggressiveness (15).

Athletes and the general public take anabolic steroid products seriously for skeletal muscle development, but their side effects are usually not appropriately followed. The side effects of these medicines may progress gradually and can lead to impairment of the body's functioning or even death. For example, among AAS consumers, who have an underlying renal disorder, severe kidney disease has been reported (11). Also, the increasing level of creatinine and BUN related to AAS can develop, and severe uremia can lead to spontaneous bleeding, such as gastrointestinal hemorrhage (reported in our patient), intracranial bleeding, internal bleeding, and consequently death (16). Another specific disorder, in this case, was DAH, which in previous studies was associated with some autoimmune disorders, like systematic lupus erythematosus and drug use (17). Alveolar hemorrhage has not been reported in previous studies and was not observed in our patient, which may be due to Universalis alopecia as an underlying autoimmune disease. Alopecia areata (AA) is one autoimmune disease at the hair follicle. AA can perform as a complete hair loss of the scalp and body, similar to AU (18). We believe that alopecia universalis as the underlying condition led to the development of these complications in this patient.

In our opinion, due to impaired body image following alopecia, the patient started bodybuilding to improve his self-concept. Furthermore, the accelerating effect that AAS products might have on increasing muscle hypertrophy encouraged him to use them. However, he was not informed about the side effects of AAS and the effect of his underlying disease on intensifying reactions. Previous studies have also shown that AAS users consume these drugs without knowing their side effects and consulting a specialist. One study in Al-Ain District among 154 gym users showed that the majority of the study populations who used AAS were informed of the desired effects of AAS, such as increases in muscular volume and body fitness, developments in body weight, and muscle power. However, only a minority knew of AAS use's health hazards. Additionally, only 13% of the users reported that their main source of AAS knowledge was a health care professional (19).

The obtained data from a study to assess the attitudes and awareness of the cardiac hazards following AAS consumption among amateur sports participants in Ireland exhibited that 59% of athletes have never been notified about the health impacts of AAS. The statics indicate that most individuals are not prepared properly to understand AAS side effects (20). Another research in Pakistan was done to analyze awareness regarding the use of AAS in the youth studying health sciences and reported that most of the participants were aware of the abuse potential of AAS, and they articulated that these drugs need to be traded by a practitioner's prescription. Therefore, it seems that physicians can significantly impact increasing the safety of AAS use (21). Saeidinejat et al. in Iran revealed that only 4.7% of 920 participants had proper information about AAS side effects (14).

Table 2. Reported adverse drug reaction cases associated with the use of anabolic steroids and herbal and dietary supplements

	Author	Age	Gender	Substance	Underlying disorders	LFT (IU/L)	Maximum SCr (mg/dl)	Complications	Outcome
1	Unai et al.(22)	42	Male	Testosterone	-	AST 58 ALT109	4.1	MODS, AKI	Recovered
2	Rosenfeld et al.(23)	50	Male	Methandrostenolone	Chronic hepatitis C	AST 61 ALT 56	3.38	Cholestatic jaundice, AKI acute pancreatitis	Recovered
3	Almukhtar et al.(24)	20	Male	Testosterone propionate nandrolone deconate	-	-	2.6	30-40 % Interstitial fibrosis and tubular atrophy of kidney	-
4	Almukhtar et al.(24)	21	Male	Testosterone proprionate nandrolone deconate	-	-	3.8	10-15% Interstitial fibrosis and tubular atrophy of kidney	-
5	Almukhtar et al.(24)	23	Male	Testosterone proprionate nandrolone deconate	-	-	3.2	Acute tubular necrosis	-
6	Almukhtar et al.(24)	26	Male	Testosterone proprionate nandrolone deconate	-	-	2.8	Interstitial fibrosis and tubular atrophy and inflammation of kidney	-
7	Flo et al.(25)	41	Male	AAS (anabolic- androgenic steroid)	-	ALT 83 AST 74	3.14	Myocardial infarction with multiorgan failure, AKI	Partial recovery
8	Bispo et al.(26)	40	Male	Trenbolone enanthate	toxic hepatitis	ALT 7125 AST 7 8 9 7	3.8	Liver failure cardiomyopathy	Partial recovery
9	Stergiopoulos et al.(13)	44	Male	Testosterone	-	AST: 86 ALT: 79	1.3	Cardiomyopathy	Partial recovery
10	Samaha et al.(27)	24	Male	AAS and Aminoacid	-	Elevated	Elevated	MODS	Not mentioned
11	Ahlgrim and Guglin(28)	41	Male	Testosterone enanthate	Resolved Cardiomyopathy	ALT191 AST 65	1.7	Cardiomyopathy	The evaluation for a heart transplant was initiated
12	Hausmann et al.(29)	23	Male	AAS	-	-	-	Sudden cardiac death	Unsuccessful resuscitation
13	Medras et al.(30)	48	Male	Metanabol Testosterone Nandrolone Parablone	-	-	-	Aortic stenosis	Unsuccessful resuscitation
14	Frakash et al.(31)	39	Male	AAS	-	-	-	Rhabdomyolysis of the deltoid muscle	Recovered completely
15	Boregowda et al.(32)	40	Male	Nandrolone Testosterone Growth hormone				Hypogonadism Erectile dysfunction Low libido	Recovered
16	Fineschi et al.(33)	29	Male	Nandrolone Testosterone Stanozolol		-	-	Sudden cardiac death	Unsuccessful resuscitation
17	Fineschi et al.(33)	32	Male	Nandrolone deconate	-	Elevate in a few days before	-	Sudden cardiac death	Unsuccessful resuscitation
18	Hardt et al.(34)	37	Male	AAS Amino acid Vitamin and mineral	-	Normal	-	Development of hepatocellular carcinoma	Recovered
19	Saharian et al.(35)	22	Male	Nandrolone deconate	-	-	-	Cerebral venous sinus thrombosis	Recovered
20 21	Froehner et al.(36) Hymel et al.(37)	32 26	Male Male	Oral-Turinabol Mastabol	arthrosis -	- ALT117	-	Intratesticular leiomyosarcoma Cholestasis	Recovered Recovered

-						ACT 70			
						AST 70 AST132			
22	Pertusi et al.(38)	28	Male	AAS	-	AST 132 ALT127	1.4	Hepatitis, rhabdomyolysis	-
						AST 21			
23	Veras et al.(39)	28	Male	Testosterone	-	AST 21 ALT 13	1.1	Impaired physical performance	Recovered
						ALT IS			Austiting Coronany
24	Kennedy(40)	24	Male	AAS	-	-	-	Myocardial infarction	Awaiting Coronary
									Angiography
25	Freeman and Rooker(41)	22	Male	Oxymetholone	-	-	-	Spontaneous rupture of the	Partial recovery
								anterior cruciate ligament	
				Stanozolol					A slight decrease in the
26	Socas et al.(42)	35	Male	Oxymetholone	-	ALT 75		Hepatocellular adenoma	size of the tumors after
				Testosterone		AST 53			4 years, improved liver
				Methenolone					function
				Stanozolol					
				Oxymetholone				Acute renal failure	
27	Socas et al.(42)	23	Male	Testosterone		AST130	10.2	Hepatocellular adenoma	Decrease in the size of
21	00003 01 01.(42)	20	Walc	Nandrolone		ALT178	10.2		the tumors after 1 year
				Boldenone					
				Diuretics					
					Crohn's disease,			Near-fetal spontaneous hepatic	
28	Patil et al.(43)	43	Male	AAS	recurrent deep vein	Normal	1.6		Recovered
					thrombosis			rapture	
				herbal and dietary					
20	Eleres et al (11)	24	Mala	supplements (HDS)			2.3	Liver dustruction AVI	Recovered
29	Flores et al.(44)	31	Male	containing anabolic	-	-	2.5	Liver dysfunction, AKI	Recovered
				androgen steroids					
				AAS					
30	Daher et al.(45)	21	Male	Vitamin A, D, E	-	-	3.9	AKI	Recovered
				supplements					
				AAS					
31	Daher et al.(45)	30	Male	Vitamin A, D, E	-	-	3.2	AKI	Recovered
				supplements					
					Aplastic anemia,				
20		00	Female	Oxymetholone (to treat	familial				
32	Nakao et al.(46)	20	(not an	aplastic anemia)	adenomatous	Normal	-	hepatic adenomas	Asymptomatic
			athlete)		polyposis				
					1 21			voice change, body hair growth,	
33	Börjesson et al.(47)	24	Female	Methenolone,	-	-		clitoromegaly, menstrual	-
	, , , ,			stanozolol				disorders	
								voice change, mood swings,	
34	Börjesson et al.(47)	16	Female	Nandrolone, stanozolol				clitoromegaly, stretch marks,	
54	Doljesson et al.(47)	10	I emaie		-	-	-	reduced breast	-
								reduced breast	
35	Börjesson et al.(47)	27	Female	Clenbuterol	-	-	-	Tachycardia, depression	-
								AKI	
						AST		Alveolar hemorrhage	
						24		GI bleeding	Unsuccessful
36	Our patient	26	Male	G-fast pills	Alopecia universalis	ALT	12.4	Pleural effusion	resuscitation
						11		Pericardial effusion	10000010000
								*The specialty of our patient is	
								having all these side effects	
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Despite the confirmed complications of IPEDs and the dangerous reactions related to their consumption, those who use IPEDs are usually hesitant to investigate professional medical consolation or visit original care services (2). On the other hand, there is no specific specialist to prescribe these substances and off-label sales of these drugs increase their availability and use. There is no specific law on selling these drugs in most countries, and they are sold in most guilds, such as shops, barbershops, fitness clubs, and even at home. Therefore, it is assumed that health care providers should consider these factors and provide a safe method of using these drugs. Therefore, due to the fatal complications and bodily harm, it will have ethical, criminal, and civil law consequences.

We recommend that the athletes take anabolic steroids under the supervision of specialists of steroid prescription, which can be preventive social health care. For this purpose, it is necessary to introduce this section as a new policy in the medical curriculum. When this method is practiced from the beginning and considered one of the duties of the medical group, society will subconsciously meet its needs in the right way.

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