

Caution for anabolic androgenic steroid use -a case report of multiple organ dysfunction syndrome.

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Short running Title: Anabolic Androgenic Steroid and multiple organ dysfunction syndromes

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Abstract

This is a report of a 42 year old male amateur body builder using anabolic androgenic steroids, who developed acute respiratory distress syndrome, acute kidney injury and refractory supraventricular tachycardia. He required extracorporeal membrane oxygenation, continuous veno-venous hemodialysis, and catheter ablation. It was thought that long-term anabolic androgenic steroid abuse predisposed the patient to developing multiple organ dysfunction syndromes from its immunomodulatory effects in an otherwise healthy patient. Anabolic androgenic steroid use should be part of the history taking process since it may complicate patient outcomes. **(Word count of abstract: 86)**

Key words: anabolic androgenic steroid, acute respiratory distress syndrome, acute kidney injury, multiple organ dysfunction syndrome, extracorporeal membrane oxygenation

Introduction

Usage of anabolic androgenic steroid (AAS) has become more common among professional and amateur athletes. The medical consequence of long term steroid abuse has remained unclear; however, there are reports of AAS abuse resulting in death.¹ We report a 42 year old male amateur body builder using AAS for muscle building who developed multiple organ dysfunction syndrome including acute respiratory distress syndrome, who required veno-venous extracorporeal membrane oxygenation (VV-ECMO).

Case Report

The patient was a 42 year old male, well built (180cm, 90kg BMI 27.8 kg/m²) amateur body builder with a previous history of smoking but otherwise having no other past medical history. He admitted to injecting himself with AAS complex's including testosterone acetate, testosterone cypionate, testosterone decanoate, testosterone propionate, testosterone phenylpropionate, testosterone enanthate and testosterone isocaproate for a few years. He presented to a local emergency room during the summer of 2012, with complaints of nausea, vomiting, diarrhea, as well as 5 days of shortness of breath and productive cough. The patient was found to be hypoxic and had episodes of supraventricular tachycardia (SVT) and rapid atrial flutter (AF) at a ventricular rate of 160 to 200 beats per minute, which was thought to be due to hypoxia. He was volume resuscitated and pharmacological anti-arrhythmic therapy was initiated, but was unable to maintain sinus rhythm. The initial diagnosis was "pneumonia", and he was started on a standard dose of ampicillin / sulbactam, vancomycin, and moxifloxacin.

He became profoundly hypoxic and was subsequently intubated on the following morning. Arterial blood gas (ABG) showed PaO₂/FiO₂ (P/F) ratio of 76 and he was diagnosed

with acute respiratory distress syndrome (ARDS). Despite optimal ventilator support, he was unable to be oxygenated and was transferred to our hospital for further management. Upon arrival, he was afebrile, was in normal sinus rhythm with a heart rate of 80 beats per minute, and a blood pressure of 111/50 mmHg. His blood pressure dropped shortly after admission and required 0.2 to 1.3 mcg/kg/min of phenylephrine to stabilize his hemodynamics. Physical exam was significant for massive edema and poor air movement; chest x-ray revealed bilateral infiltrates (Figure 1). He was placed on assist control mode ventilation with 100% FiO₂ and 15cmH₂O of PEEP. The ABG was pH 7.26, pCO₂ 40mmHg, PaO₂ 67mmHg, base deficit 8.2, SatO₂ 88%. The peak airway pressure was 36 cmH₂O. Other laboratory data showed WBC 10.8 (Bands 15%) B/L, Hb 13.2g/dl, Plt 185B/L, INR 1.39, PTT 24 sec, Ca 3.6mg/dl, Na 140mEq/L, K 5.5mEq/L, Cr 3.8mg/dl, T.bil 0.4mg/dl, AST/ALT 2335/1458 IU, procalcitonin 7.51ng/ml, CRP 26.7mg/dl (Table 1). Urine toxicology screen test was negative; echocardiography showed normal systolic and diastolic left and right ventricular function without any evidence of intra-cardiac shunting or valvular disease; abdominal ultrasound was normal.

Due to profound hypoxia, veno-venous extracorporeal membrane oxygenation (VV-ECMO) was initiated using the Avalon cannula (Avalon Laboratories, Rancho Dominguez, CA). He was placed on low tidal volume (4-6ml/kg ideal body weight) ventilation based on ARDSnet protocol², and the plateau airway pressure was kept at 20-25 cm H₂O. His oxygenation was controlled with ECMO aiming at upper extremity arterial saturation above 85%. Cerebral saturation was kept over 50% using Fore-sight tissue oximetry (Casmed, Branford, CT) to ensure cerebral perfusion.³ The antibiotic regimen was changed to piperacillin / tazobactam 3.375g IV q8 hours and moxifloxacin 400mg IV qday. The patient was oliguric and massively

volume overloaded, and was diagnosed with acute kidney injury (AKI) and continuous veno-veno hemodialysis (CVVHD) was initiated for fluid removal. Multiple cultures of blood, bronchial lavage and urine, including those from the outside hospital before antibiotic therapy was initiated, were negative. HIV 1/2 antibody, virus PCR for influenza A, B/ parainfluenza 1-3 / rhinovirus / enterovirus / metapneumovirus / adenovirus / respiratory syncytial virus, hepatitis B surface antigen, hepatitis C antibody, antigen tests for *legionella pneumophila* and *streptococcal pneumoniae* were also negative. Due to these test results, antibiotics were discontinued on day 7. His respiratory status and chest x-ray gradually improved (Figure 2), and VV-ECMO was discontinued on day 7. Following discontinuation of VV-ECMO, his ABG was pH 7.39, pCO₂ 43mmHg, PaO₂ 69mmHg, SatO₂ 93% on assist controlled ventilation with 60% FiO₂ and 12cmH₂O of PEEP. The patient started to make urine and CVVHD was discontinued on day 9 and intermittent hemodialysis was discontinued on day 11. During his hospital stay, he had multiple episodes of SVT and AF. A diltiazem / amiodarone protocol was initiated and IV metoprolol was given, but the patient failed to maintain in sinus rhythm. Electrical cardioversion and adenosine were able to convert to sinus rhythm, but he returned to SVT or AF in a short period of time. After his oxygenation improved, he was taken to the electrophysiology lab and cava tricuspid isthmus was ablated for AF. Afterwards, further electrophysiology studies were performed, but SVT was not able to be induced; thus, no additional ablation was done. He was placed on oral amiodarone and diltiazem, and was able to maintain sinus rhythm afterwards. Tracheostomy was performed on day 20 due to ventilator dependency; however, he was able to come off ventilator on day 27. His nausea and vomiting persisted during the hospital stay, but resolved gradually. The tracheostomy was removed prior

to discharge to home on day 38.

Discussion

The use of AAS among professional athletes and bodybuilders has been reported since the 1950s.⁴ Gradually it became more popular among recreational and non-professional bodybuilders. In 1980s, AAS had gained popularity among young males for purposes to increase muscle mass and physical appearance.⁵ Currently, AAS use has spread to casual fitness enthusiasts and sub-elite sportsmen and sportswomen since AAS can be obtained via the internet without a prescription. It is estimated that there are three million AAS users in the USA and the lifetime prevalence of AAS use is 0.9% for males and 0.1% for females in general population.⁵

The medical effects of long-term AAS abuse are unclear. The known common side effects include acne, testicular atrophy, gynecomastia and pain at the injection site. Erectile dysfunction and libido loss may also occur.⁶ Nausea and vomiting, as seen in our case, has been reported in several case reports.^{6,7} The mechanism of the chronic nausea and vomiting in AAS users was considered to be related to hypercalcemia, which was induced by AAS⁸, but it was not seen in our case. Other less common but severe side effects include cardiovascular complications, hepatic dysfunction, AKI, psychiatric disorders, reduction of thyroid hormone production, infertility and immunomodulatory effects.^{6,9} Mortality risk among chronic AAS users is estimated to be 4.6 times higher than normal age-adjusted population.⁴

Herr reported a 30 year old bodybuilder who developed ARDS secondary to sepsis from an abscess at the injection site.¹⁰ The authors suggested that the long term use of AAS caused an immunosuppressive effect and resulted in sepsis in an otherwise healthy patient. In our case, despite extensive workup, the etiology of ARDS remained unknown. One differential diagnosis

was aspiration pneumonia caused by persistent nausea and vomiting. Elevated WBC and procalcitonin suggested bacterial infection, but all the cultures were negative. Voigt reported that an respiratory syncytial virus infection resulted in ARDS in an HIV infected adult patient.¹¹ A viral infection may have been the cause of nausea, vomiting and diarrhea prior to the hospital visit in this presented case. The patient may have had a micro-aspiration while he had these symptoms. It was a possible that the combination of an undetected viral infection and aspiration caused a septic picture and it was multiplied by the immunosuppressive effect of long term AAS abuse, which leads to ARDS. Injection of supraphysiological concentrations of AAS suppresses natural killer cell activity and lymphocyte development into effector and memory cells, which subsequently decreases antibody sensitivity and secretion, resulting in an immunosuppressive effect.⁹

The treatment of ARDS consists of fluid management, protective lung ventilation with low tidal volumes and moderate PEEP, multi-organ support and treatment of the underlying cause. ECMO is indicated for ARDS in case of severe hypoxemia ($\text{PaO}_2/\text{FiO}_2 \leq 80$ mmHg, despite high PEEP), uncompensated respiratory acidosis ($\text{pH} < 7.15$, $\text{PCO}_2 > 60$ mmHg), and/or unable to tolerate conventional mode of mechanical ventilation.¹² The Avalon cannula is designed for VV-ECMO, drawing de-oxygenated blood from the superior / inferior vena cava and returning oxygenated blood toward the tricuspid valve. Contraindications of the use of Avalon cannula are intra-cardiac shunting or other general contraindications of ECMO such as intracranial bleeding.

There are few reports that have shown a possible effect of AAS use and altered cardiac electrical activity. The use of AAS has been reported to increase the rate of cardiac

repolarization and shortening of the QT interval.¹ Myocardial structural and molecular remodeling induced by AAS are also reported and it can lead to severe atrial arrhythmia,¹³ as observed in our case. Other cardiovascular complications on AAS users that have been reported are acute myocardial infarction related to premature atherosclerosis caused by increased low-density lipoprotein cholesterol and decreased high-density lipoprotein cholesterol.⁴ There is an increased risk for arterial and pulmonary embolism due to elevated hemoglobin levels.¹ Additionally, impaired left ventricular systolic and diastolic function may develop secondary to direct toxic effects on myocytes, endothelial cells and / or increased collagen crosslinks between myocytes. The clear mechanisms of AAS induced arrhythmia remains unknown.

In physiological state, serum creatinine level is proportional to body muscle mass, and those who have well developed musculature may have higher baseline serum creatinine dependent on clearance. AKI may be triggered if any of the following condition occurs: dehydration and rhabdomyolysis caused by strenuous exercise, use of non-steroidal anti-inflammatory drugs to ease the musculoskeletal pain related to exercise, use of diuretics to reduce weight; to maintain muscular body habitus and to clear banned substances from urine. Daher reported two cases of AAS related interstitial nephritis causing AKI.⁶ Habscheid and Yoshida separately reported a type of AAS (Stanozolol) causing cholestasis that resulted in AKI in an otherwise healthy young male.^{14, 15} They thought that AAS abuse caused cholestasis and jaundice, which subsequently caused decrease of systemic vascular resistance and hypotension, hypoperfusion of the kidney, leading to AKI. In our case, the AKI could be due to the combination of persistent hypoxia and sepsis.

The liver enzymes were only slightly elevated when he presented at the outside hospital,

but were elevated when the patient was transferred to our hospital. We believe this transient liver dysfunction was related to the combination of hypoxia and septic condition, rather than direct toxicity from AAS abuse. Although his echocardiography was normal, multiple episodes of SVT and massive fluid resuscitation for low blood pressure, acute kidney injury associated with low urine output, may have resulted in fluid overload and hepatic congestion. His NT proBNP was mildly elevated upon admission to the outside hospital (917.8pg/ml) and the existence of a pleural effusion on echo, support this assumption. However, it would be unusual that the cause of hypoxia was cardiogenic pulmonary edema, as he was rather dehydrated/hypovolemic when he arrived at the outside hospital, and echo showed good left ventricular function. The liver enzymes quickly improved, after correction of the volume status, and the initiation of VV-ECMO and CVVHD.

Conclusions

Although there is only limited literature regarding AAS use and their side effects, long term AAS use may lead to serious health consequences. The direct relation of AAS and multi-organ dysfunction is unclear in our case, it is reasonable to believe that the long standing history of AAS abuse played a great role in causing systemic inflammatory response syndrome and multiple organ dysfunction syndromes in an otherwise healthy patient.

Table 1. Laboratory values of the patient.

	admission at outside hospital	6 hr after intubation	admission to our hospital	after VV-ECMO	3 days after VV-ECMO	1 day after VV-ECMO decannulation	before discharge
WBC (B/L)	12.5	8	10.8	12.2	25.6	14.7	16.8
HGB (g/dl)	16.2	13.4	13.2	11.1	9.9	9.7	8.7
HCT (%)	45.7	39.5	40.7	34.6	29.5	27.9	26.5
PLT (B/L)	246	206	185	231	234	131	454
FiO ₂ of ventilator	100%	100%	100%	100%	50%	60%	Room air
Mode of ventilator	NR mask	AC PEEP 5	AC PEEP 15	AC PEEP 10	AC PEEP 10	AC PEEP 12	
FiO ₂ of VV-ECMO				100%	60%		
PH	7.56	7.37	7.26	7.39	7.38	7.39	
pCO ₂ (mmHg)	25.5	40.7	40	44	48	43	
pO ₂ (mmHg)	50	76	67	81	104	69	
HCO ₃ (mEq/L)	23	23	18	26	28	26	
BE (mEq/L)	3	-1	-8.2	1.8	3.1	1.3	
SatO ₂ (%)	91	93	88	96	98	93	98
Na (mEq/L)	135	139	140	144	137	137	137
K (mEq/L)	4	4.4	5.5	4.8	4.7	3.8	3.8
Cl (mEq/L)	97	104	108	109	105	101	102
BUN (mg/dl)	20	27	49	52	23	39	35
Creatinine (mg/dl)	1.57	2	3.8	4.1	2.7	2.4	2.2
Glucose (mg/dl)	131		172	170	134	87	98
T. Bil (mg/dl)	3.4	0.3		0.4	0.7	1.3	0.9
AST (IU/L)	58	46		2335	94	53	16
ALT (IU/L)	109	67		1458	387	159	24
Lactate (mmol/L)	1.9	0.7	2.2	2.3		1.2	

AC: assist control; NR non-rebreasing mask with 100% oxygen; VV-ECMO: veno-veno extracorporeal membrane oxygenation

Legends of Figures

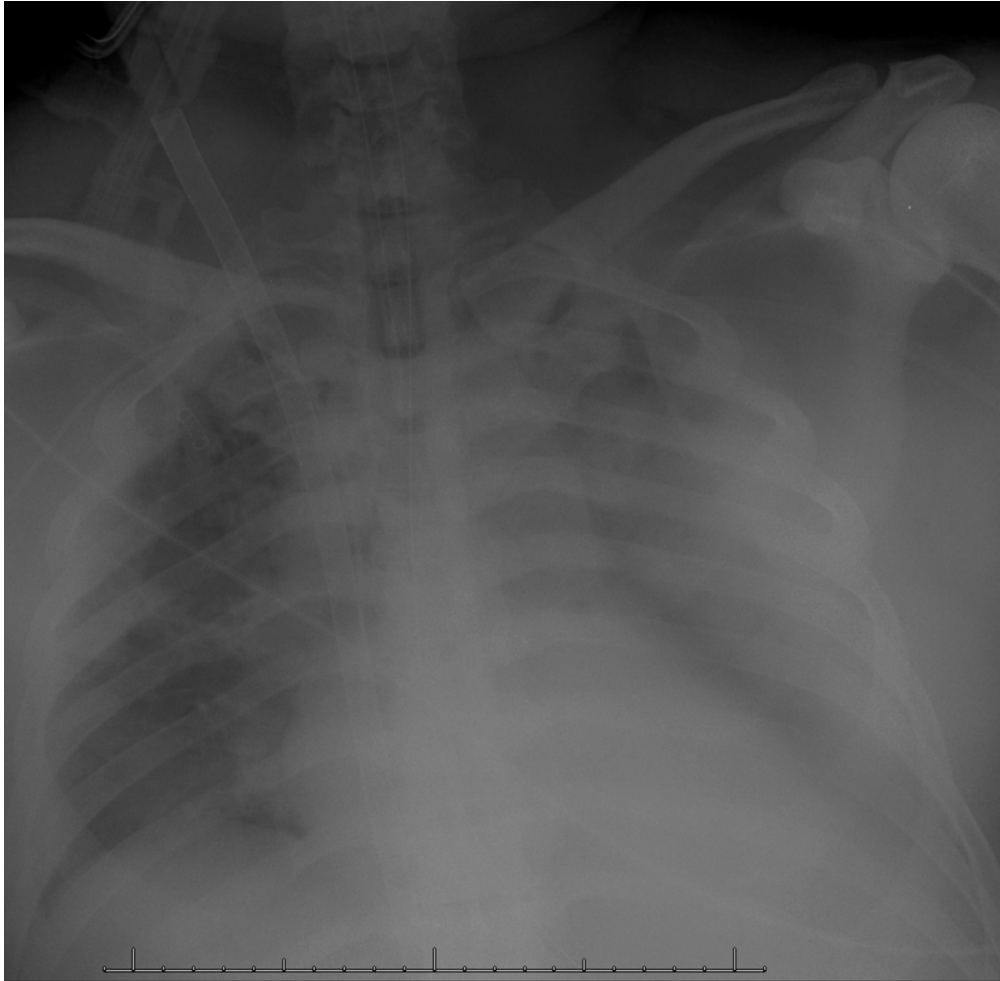
Figure 1: Chest x-ray on admission shows bilateral infiltrates.

Figure 2: Chest x-ray before discharge shows clear lung fields.

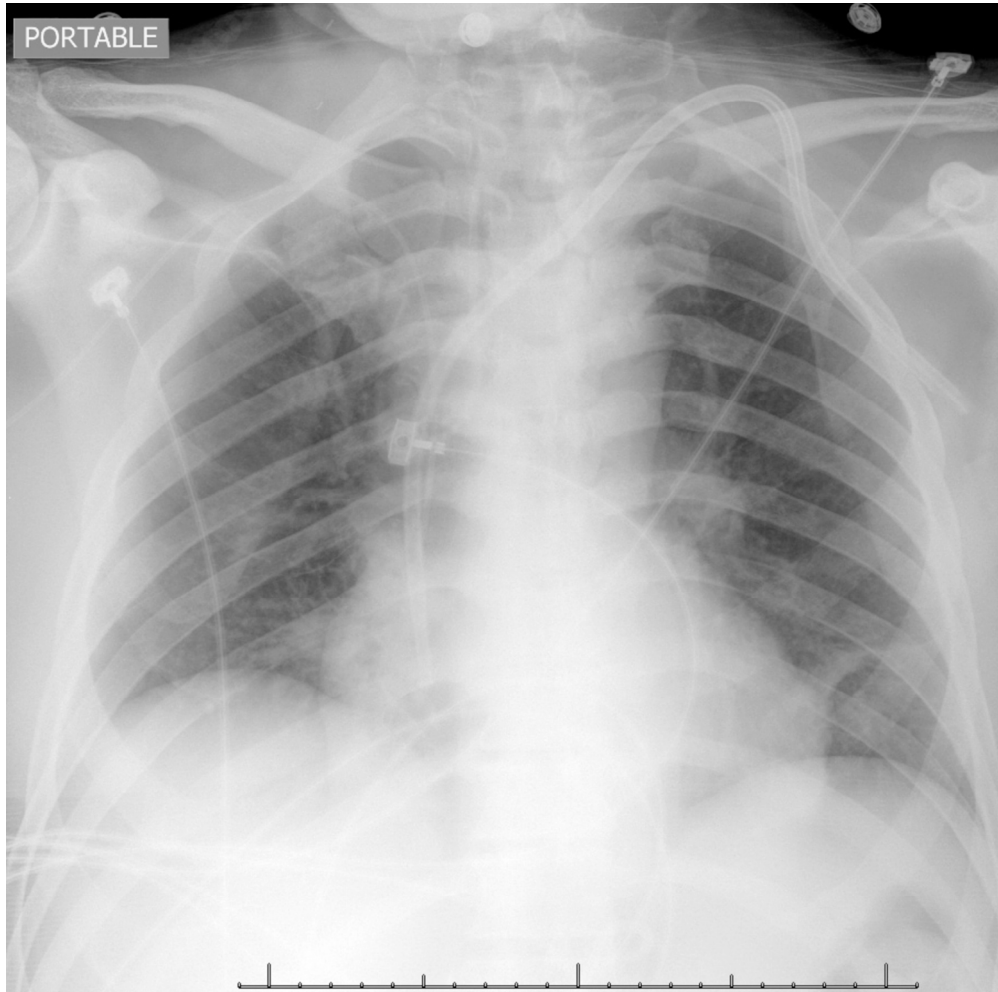
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Initial chest x-ray shows bilateral infiltrates.
127x124mm (300 x 300 DPI)



Chest x-ray before discharge shows clear lung fields.
127x125mm (300 x 300 DPI)