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Case Report

Adrenal Insufficiency in a Mosaic Klinefelter Syndrome

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Abstract

We report a rare presentation of Klinefelter with an adrenal insufficiency diagnosed in a late stage of life. A 52 years old white male was admitted to MICU after a suicidal attempt by drinking three bottles of isopropyl alcohol. The patient presented with lethargy and altered mental status, and severe hypothermia of 34.5°C as he was found exposed during a snowstorm. Later, he was admitted to MICU with severe hypotension that was treated with fluid challenge and pressors. Cosyntropin test revealed hypoadrenalism. The patient disclosed a condition of Mosaic karyotype of Klinefelter syndrome, which was attributed as a cause of his hypoadrenalism.

Keywords: *Klinefelter Syndrome; Mosaic Karyotype; Adrenal Insufficiency*

Introduction

Klinefelter syndrome is one of the sex chromosome disorders and it occurs in one of every 600 newborn males [5]. It occurs in males who have at least one extra X chromosome, XXY. Klinefelter syndrome is a common congenital anomaly that causes primary hypogonadism. Also, it can cause hypoadrenalism occurring in approximately 1 in 1000 live male births [11]. The most common genotype is 47, XXY, but greater and lesser numbers of X chromosomes have also been reported, resulting in different karyotypes such as 48, XXXY and 46, XY/46, XXY mosaicism [7]. 46, XX men also have Klinefelter syndrome; the development of testes is mainly due to translocation of a minimal portion of chromosomal material having the testis-determining factor to an X chromosome. The 47, XXY genotype comes from the non-disjunction of either parent's sex chromosomes at the meiotic division. The mosaicism occurs as a result of incomplete division at mitoses division after conception. The greater the number of extra X chromosomes, the greater the phenotypic consequences, both gonadal and extra-gonadal [16]. The clinical features differ by developmental stage and severity of phenotype. Presentations are almost invariably small, firm testes, low sperm count, infertility, increased serum FSH and LH levels, lower serum testosterone concentration, and decreased virilization. A prolonged bone abnormality, resulting in increased length of the legs, independent of the increased length of both the arms and legs caused by testosterone deficiency. There is a significantly increased risk of Addison's disease with a rate ratio of 11.7, 95% confidence interval [15]. As seen in our case, the patient presents with symptoms of primary partial or complete adrenal insufficiency. There are a number of genes located on the X chromosome that regulate the function of the immune system [4]. It is possible that the genes on the additional X chromosomes that escaped inactivation in KS might increase the risk of autoimmune diseases as there case reports suggesting that some autoimmune diseases may be more common in KS patients than in others [4,17].

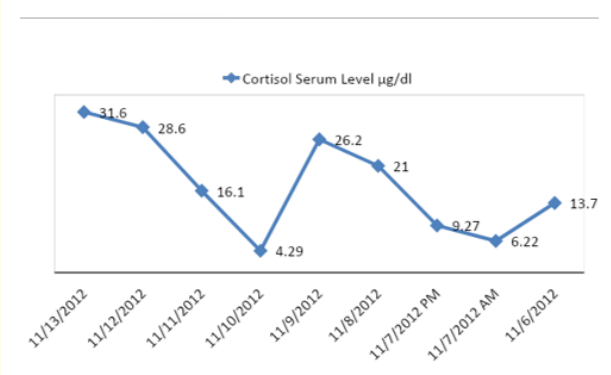
Patients with chronic primary adrenal insufficiency may have symptoms and signs of glucocorticoids, mineralocorticoid, and androgen deficiency. The diagnosis is usually evident in patients with the full-blown syndrome of adrenal insufficiency. The syndrome onset is variable. In its early stage, therefore, diagnosis may be difficult [14]. The most common clinical features of chronic primary adrenal insufficiency include chronic malaise, lassitude, fatigue, generalized weakness, anorexia, and weight loss. Weight loss is primarily due to anorexia, but dehydration may contribute. The amount of weight loss can vary from 2 to as much as 15 kg and may not become evident until adrenal failure is advanced [11]. Clinical manifestations of gastrointestinal symptoms can present as nausea, vomiting, abdominal pain, diarrhea that may alternate with constipation. These symptoms are common and correlate with the severity of adrenal insufficiency. Vomiting and abdominal pain often herald adrenal crisis. Also, cardiovascular symptoms can present as postural dizziness, syncope, hyponatremia, hyperkalemia, mild hyperchloremic acidosis. Other symptoms like hypoglycemia may occur yet is rare in adults in the absence of infection, fever, or alcohol ingestion. This would be attributed to an increase in patient's sensitivity secondary to loss of the gluconeogenic effect of cortisol and the hyperglycemic effects of epinephrine, hyperpigmentation in sun-exposed areas secondary to release of Melanocyte stimulating hormone [2].

A psychosocial abnormality unrelated to hypogonadism causes difficulty in social interactions throughout life, presenting a marked lack of insight, poor judgment, and impaired ability to learn from adverse experiences. Also, impairment of higher-level linguistic competence spares vocabulary and understanding of language and a deficit in sustaining attention without impulsivity [18].

Case Summary

A 52-year-old white male patient was admitted to the medical intensive care unit (MICU) with the diagnosis of severe hypotension and hypothermia after a suicidal attempt of consuming three bottles of Listerine. The patient has a 38 years history of smoking with an average of 20 cigarettes per day and occasional alcohol consumption but no recreational drug abuse. The patient had no past medical history except for Mosaic Klinefelter syndrome that was diagnosed years ago. The patient revealed a history of low sodium levels and blood glucose in the last few months. He was brought to the emergency department after being found undressed and intoxicated in severe cold weather conditions.

Physical exam was unremarkable except for marked pallor, patchy hyperpigmentation, tall stature with absent male hair patterns, and feminine hair distribution, in addition to the small testis, hypospadias, and no palpable organomegaly. The patient was severely hypotensive on arrival; blood pressure 85/40 mmHg and pulse 110 beats per minute. The patient was treated with 2 liters bolus and Levophed. The patient's blood pressure was maintained at 120/80 mmHg supine and 100/55 mmHg semi-sitting and pulse 130 beats per minute and respiratory rate of 19 breaths per minute.



Graph 1: : *Cortisol level during the course of admission.*

HEMATOLOGY / Day	11/6/2012 7:30	11/6/2012 14:00	11/7/2012 4:57	11/8/2012 4:00	11/9/2012 11:00	11/12/2012 9:45
WBC	15.10 H	9.6	11.70 H	12.60 H		6.6
RBC	4.28	3.68 L	3.49 L	3.51 L		3.85 L
HGB	14.1	12.0 L	11.6 L	11.2 L		12.5 L
HCT	41.8	36.1 L	34.0 L	34.5 L		37.7
MCV	97.6	98	97.4	98.2		98
MCH	33.0 H	32.6 H	33.2 H	32		32.5 H
MCHC	33.8	33.3	34.1	32.6		33.2
RDW	13.5	13.7	13.7	13.5		13.7
MPV	7.3 L	6.9 L	7.2 L	7.4		8.1
Platelet Count	746 H	524 H	485 H	482 H		421
Neutrophils Automated	69	69.3	70	71.7		54.9
Lymphocytes % Automated	25.5	26.9	25.3	23.9		33.8
Monocytes % Automated	3.3 L	3.1 L	3.4	3.6		7.1
Eosinophils Automated	1.1	0.5 L	1.1	0.0 L		3.3 H
Basophils Automated	1.1 H	0.2	0.2	0.8		0.9 H
Segs, Absolute	10.40 H	6.6	8.20 H	9.00 H		3.6
Lymphs, Absolute	3.8	2.6	3	3		2.2
Mono, Absolute	0.5	0.3	0.4	0.4		0.5
Eos, Absolute	0.2	0	0.1	0		0.2
Basos, Absolute	0.20 H	0	0	0.1		0.1
COAGULATION						
Prothrombin Time	10.7		12.1	11.4		
INR	1.0*		1.1*	1.0*		
PTT	35.1*		34.6*	32.1*		
CHEMISTRY						
Glucose	66 L	109 H	130 H	83	112 H	
BUN	14	11	7.0 L	10	12	
Creatinine	0.50 L*	0.60 L*	0.60 L*	0.50 L*	0.60 L*	
Sodium	129	131	135	140	145	
Potassium	5	3.8	3.8	3.7	3.5	
Chloride	105	110 H	109 H	110 H	110 H	
CO2	26	24	25	26	23	
Calcium	9.7	8.3 L	8.1 L	9.1	9	
Phosphorus		4.4	4.1	4.3		
Total Protein	7.5	5.7 L	5.4 L	5.4 L		
Albumin	4.9	3.6	3.2 L	3.2 L		
Bilirubin	0.5	0.5	0.6	0.5		
ALT (SGPT)	71	56	46	44		
AST (SGOT)	66 H	45	36	19		
Alkaline Phosphotase	110	86	68	82		
Magnesium		1.6	1.8	1.8		
Lactic Acid		0.8		1		
Alchohol	12.00 H			<10.00		
Anion Gap	13.00*	8	9	7	12	
Anion Gap with K	18.00 H	11.8	12.8	10.7	15.5	
Osmolality	332 H		310 H	311 H		
ENDO & NUTR						
TSH		0.759				
Thyroxine Free		1.19				

Table 1: *Serial blood test results.*

The patient was treated with hydrocortisone 50 mg PO three times a day and a sodium-rich diet. His Levophed requirements went dramatically down from 18 mcg/min to zero mcg one day after the initiation of Levophed. Endocrinology evaluation was performed and suggested that the mosaic pattern of Klinefelter syndrome leads to late-onset adrenal failure. Also, to be noted that psychiatry cleared the patient.

Discussion

We noticed multiple findings attributed to adrenal failure, which surprisingly occurred in the late stage in life after his suicidal attempt. These findings include the following: hypospadias, testicular atrophy, patchy hyperpigmentation, depression, chronic hyponatremia, and hypotension that resolved on glucocorticoid replacement in the form of hydrocortisone. At the same time, sodium was adequately maintained by diet alone. The patient also was treated with a testosterone patch. Consequently, he started to have a more male hair distribution and better psychosocial state after improving his secondary sexual characters [10].

The causes of primary adrenal insufficiency have been changed over time due to different reasons. Before 1920, the main etiology of primary adrenal insufficiency was tuberculosis, but now it only accounts for only 7 to 20% of cases [14]. Since 1950, most cases were due to autoimmune adrenalitis, either isolated or as part of a poly-glandular syndrome [3]. Causes of adrenal insufficiency would be attributed to autoimmune adrenalitis; this condition results from an autoimmune process that destroys the adrenal cortex involving both humoral and cell-mediated immune mechanisms. It may present in isolation or may be accompanied by other diseases such as infectious adrenalitis; many infectious agents may attack the adrenal gland and result in adrenal insufficiency such as tuberculous adrenalitis), severe fungal infections and HIV-related infections, e.g. adrenalitis associated with cytomegalovirus as well as *Mycobacterium avium* complex. Another cause can be hemorrhagic infarction, a bilateral adrenal infarction caused by hemorrhage, or adrenal vein thrombosis may also lead to adrenal insufficiency [9]. Other reasons such as coagulopathies, heparin-induced thrombocytopenia syndrome, antiphospholipid syndrome have been associated with adrenal vein thrombosis and hemorrhage [2]. Adrenal hemorrhage is also common in meningococcemia (Waterhouse-Friderichsen syndrome) and Pseudomonas aeruginosa infection.

Moreover, adrenoleukodystrophy is an X-linked recessive disorder affecting 1 in 20.000 males. It is characterized by spastic paralysis and adrenal insufficiency, usually beginning in infancy or childhood, and is caused by mutations in the ABCD1 gene, resulting in defective beta-oxidation of very-long-chain fatty acids (VLCFAs) within peroxisomes [12,13]. Lastly, drug-induced adrenal insufficiency may be secondary to inhibiting cortisol biosynthesis, particularly in individuals with limited pituitary or adrenal reserve, include aminoglutethimide (antiepileptic) etomidate (anesthetic-sedative), ketoconazole (antimycotic), and metyrapone drugs that accelerate the metabolism of cortisol and most synthetic glucocorticoids by inducing hepatic mixed-function oxygenase enzymes, such as phenytoin, barbiturates, and rifampicin can also cause adrenal insufficiency in patients with scarce pituitary or adrenal reserve, also those on hormone replacement therapy. Furthermore, some novel tyrosine kinase-targeting drugs (e.g. sunitinib) have been shown in animal studies to cause adrenal dysfunction and hemorrhage [3,10].

Critical illness-related corticosteroid insufficiency is characterized by dysfunction of the hypothalamic-pituitary axis (HPA) during critical illness. In sepsis or septic shock cases, this syndrome results from adrenal insufficiency combined with glucocorticoid resistance [8].

Conclusion

Due to the rarity but seriousness of the encountered cases, more research input must be geared towards exploring various associated presentations and potential complications related to this syndrome. Furthermore, an establishment of solid management guidelines must be proposed, especially if a concomitant comorbidities are present.

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