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Case Report

Is Bilateral Orchiectomy for Metastatic Prostate Cancer Treatment Associated with High Cardiovascular Risc?

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ABSTRACT: Cardiovascular disease is one of the most common causes of death worldwide and the most usual in the western populations. Although it affects both sexes, it is more frequent in males in whom it shortens the average life expectancy. This difference has been attributed to the negative effects of testosterone; however, recent research showed that this hormone may have protective effects on the cardiovascular system. In confirmation to the above current evidence suggests that the low levels of testosterone could be associated with an increased CVD risk and with an augmentation of morbidity and mortality in males. In the present article, we present 2 cases of men with CVD and metastatic prostate cancer treated with bilateral orchiectomy who died of acute stroke during the perioperational period. The possible association of androgen deprivation with cardiovascular disease progression and the consequent risk of stroke are briefly discussed.

Key words: Orchiectomy; Metastatic Prostate Cancer; Cardiovascular Risc

Despite the development of a variety of novel agents for the treatment of advanced and metastatic prostate cancer, the foundation of treatment for this stage of disease remains androgen-deprivation hormonal therapy. The last is either surgical (orchiectomy) or medical (luteinizing hormone–releasing hormone [LHRH] antagonists, LHRH agonists and antiandrogens) [1]. Considerable emotional and psychologic effects render orchiectomy unacceptable to most patients and thus the abovementioned medications are usually used as primary hormonal therapy. In contrast, orchiectomy is rarely performed although it is a simple and virtually complication-free surgical procedure; it is easily performed under local anaesthesia and is cost effective. However, when initial relapse on hormonal therapy occurs despite medical treatment, orchiectomy may be an option for patients with serum testosterone levels higher than 50 ng/dL (castration levels). In fact, about 10% of patients treated with LHRH agonists fail to achieve castration levels. This proportion rises to 15% if the castration threshold is defined as 20 ng/dL [2].

Bilateral orchiectomy, which is either total or subcapsular (i.e. with preservation of tunica albuginea and epididymis) is the quickest way to achieve a castration level, usually within less than 12 hours [3]. Exposure to LHRH agonists and antagonists eventually results in down-regulation of LHRH-receptors, suppressing pituitary LH and FSH secretion and testosterone production. Testosterone levels decrease to castration levels usually within 2-4 weeks [4].

Presentation of cases

1) Patient demographics and prior history

Their median age was 79,5 years. The older patient was a diagnosed with occult prostate cancer 18 years prior to his admission for which he was treated with watchful waiting. He reported arterial hypertension under treatment and a left nephrectomy 36 year prior his admission for renal abscess treatment. The younger one was diagnosed with

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locally advanced prostate cancer 7 years prior to his admission for which he was treated with external radiotherapy and adjuvant androgen-deprivation hormonal therapy. Upon biochemical relapse he received LHRH agonists and antiandrogens. Despite treatment his PSA value raised to 50ngr/ml. He was suffering of serious CVD, hypertension and type 2 diabetes.

2) Detailed clinical features

Case 1: A 86-year-old vegetarian man with a history of prostate cancer and an interrupted watchful waiting treatment presented with urinary retention and back pain. On clinical examination his prostate was irregularly enlarged and hard in palpation. Upon examination he reported suprapubic discomfort and pain in the right costo-vertebral angle. Abdominal ultrasound revealed dilatation of the renal pelvis and ureter and residual urine of 750 cc. Blood urea nitrogen (BUN) and serum creatinine level were elevated (96 and 1,8 respectively) while his serum PSA value was 120 ngr/ml. CT scan of the abdomen revealed a large prostate protruding in the urinary bladder lumen while the bone scan revealed metastatic lesions on the O2 and O3 vertebras. Preoperative ECG revealed a scar due to a silent heart attack some time ago. He was treated with bilateral subcapsular orchiectomy under general anaesthesia. No complications occurred. He recovered rapidly and he discharged home the 2nd postoperative day. He died at home, in his sleep 3 days after the operation. In autopsy, the cause of death was attributed to acute stroke.

Case 2: A 73-year-old male smoker with a history of locally advanced prostate cancer and biochemical relapse presented with gross hematuria. On clinical examination his prostate was small and hard in palpation. He reported no pain or discomfort in the clinical. Abdominal ultrasound and CT scan were normal. BUN and serum creatinine level were normal while his serum PSA value was 50 ngr/ml. The bone scan revealed metastatic lesions on the 5th and 6th ribs. Patient refrained from aspirin for one week before surgery. He was treated with bilateral subcapsular orchiectomy under spinal analgesia. No infection or bleeding occurred, however he died the 2nd postoperative day from an acute stroke, despite prophylactic low molecular weight heparin administration.

DISCUSSION

CVD is one of the most common causes of death worldwide and the most usual in the western populations. Although it affects both sexes, it is more frequent in males in whom it shortens the average life expectancy. In the past, this difference has been grossly attributed to the negative effects of testosterone. Nowadays, an amount of evidence suggests that this hormone may have protective effects on the cardiovascular system: during the last decade low testosterone was associated with conditions that predispose to CVD such as excess abdominal fat [5,6] and atherosclerosis [7,8]. In fact, a critically important role of testosterone is to enable HDL to remove excess cholesterol from the arterial wall and transport it to the liver for disposal. This effect of enhancing HDL termed "reverse cholesterol transport" is vital to preventing arterial occlusion [9,10].

However still there are no solid proofs of an association between testosterone levels and CVD and indeed, the literature provides no clear answer as to whether low endogenous testosterone increases risk of CVD in healthy men. An older metanalysis suggests that evidence weakly supports the inference that testosterone use in men is not associated with important cardiovascular effect [11]. However, when examined separately for age groups, testosterone seems to be associated with CVD risk: in a recent metanalysis, while no association between endogenous testosterone levels and risk for CVD in middle-aged men was found, it was showed that testosterone may protect elderly men against CVD [12]. On the other hand, it is believed that low testosterone may indicate a poor general health and therefore, associations between testosterone and CVD are coincidental. In fact, conventional risk factors for cardiovascular disease in men (e.g. diseases such as metabolic syndrome, aortic and lower limb arterial disease and clinical findings such as increased carotid intima-media thickness loss of insulin sensitivity [13,14] have been associated with lower circulating testosterone concentrations [15]. Moreover, a number of additional independent risk factors involved in the development of atherosclerosis, thrombosis and subsequent heart attack and stroke exists, rendering thus the above association difficult. To our knowledge, Yeap et al., in a respectively large prospective study, after adjusting for conventional risk factors for cardiovascular disease, demonstrated that lower total testosterone levels predict increased incidence of stroke in older men [16]. Similarly, Muller et al., showed that low free testosterone levels were related to intima-media thickening of the common carotid artery in elderly men independently of cardiovascular risk factors [17].

It remains unclear how low testosterone levels trigger major cardiovascular events and it is not known if a drammatical reduction of circulating testosterone can lead to lethal acute stroke. In contrast it is well known that estrogens cause deep venous thrombosis in about one-third of male patients while 7% of them experience myocardial infarction. The incidence of these complications is dose depended and increases in patients

with CVD [18]. In confirmation to the above, Callou de S áet al., found that men with CVD have higher oestradiol and FEI levels [19]. In fact, elevated estrogen can sharply increase heart attack risk by promoting platelet aggregation and coagulation in coronary arteries [20]. Higher estrogen in men also increases inflammation which can cause unstable plaque to rupture and occlude a coronary artery, thus creating a sudden heart attack [21,22].

However, it is not clear how estrogens contribute to CVD development in the elderly. On one hand, it has long been known that aging men have a propensity to develop high levels of estrogen combined with woefully inadequate testosterone [23]. On the other hand most aging men suffer both low testosterone and estrogen [24]. The most possible explanation of this controversy is that estrogens act on cardiovascular system even at low quantities. Moreover, aging men are at risk for having excess activity of aromatase. The effect of surplus aromatase is that most testosterone is converted to estrogen [25]. Given that many aging men suffer from CVD, it seems plausible that in the elderly, an imbalance between endogenous testosterone and estrogen may contribute to CVD deterioration. Of note, recent studies showed that the lower testosterone the higher estrogen levels and the subsequent risk of CV mortality [26]. Taking in account the above considerations it could be easily assume that the rate of testosterone decline is of outmost importance: Elder prostate cancer patients suffering of CVD who receive androgen-deprivation medical therapy may develop gradual increment of CVD risk with the gradual decline in total testosterone levels. In contrast those undergoing bilateral orchiectomy are in immediate risk due to rapid drop of testosterone levels.

CONCLUSION

Further studies are warranted to determine whether interventions that raise estrogen levels might affect CVD disease risk in men. Moreover, clinicians need to be aware of the serious risk of CVD complications when deciding the type of androgen deprivation therapy in aged CVD patient with prostate cancer.

References

[1] McLeod DG (2003). Hormonal therapy: historical perspective to future directions. Urology, 61(2 Suppl 1):3-7.

[2] Crawford ED, Tombal B, Miller K, Boccon-Gibod L, Schr öder F, Shore N, et al (2011). A phase III extension trial with a 1-arm crossover from leuprolide to degarelix: comparison of gonadotropin-releasing hormone agonist and antagonist effect on prostate cancer. J Urol, 186:889-97.

[3] Desmond AD, Arnold AJ, Hastie KJ (1988). Subcapsular orchiectomy under local anaesthesia. Technique, results and implications. Br J Urol, 61:143-5.

[4] Klotz L, Boccon-Gibod L, Shore ND, Andreou C, Persson BE, Cantor P, et al (2008). The efficacy and safety of degarelix: a 12-month, comparative, randomized, open-label, parallel-group phase III study in patients with prostate cancer. BJU Int,102:1531-8.

[5] Chen RY, Wittert GA, Andrews GR (2006). Relative androgen deficiency in relation to obesity and metabolic status in older men.Diabetes Obes Metab, 8:429-35.

[6] Boyanov MA, Boneva Z, Christov VG. Testosterone supplementation in men with type 2 diabetes, visceral obesity and partial androgen deficiency. Aging Male (2003), 6:1-7.

[7] Hak AE, Witteman JC, de Jong FH, Geerlings MI, Hofman A, Pols HA (2002). Low levels of endogenous androgens increase the risk of atherosclerosis in elderly men: the Rotterdam study. J Clin Endocrinol Metab, 87:3632-9.

[8] Jones RD, Nettleship JE, Kapoor D, Jones HT, Channer KS (2005). Testosterone and atherosclerosis in aging men: purported association and clinical implications. Am J Cardiovasc Drugs, 5:141-54.

[9] Langer C, Gansz B, Goepfert C, et al (2002). Testosterone up-regulates scavenger receptor BI and stimulates cholesterol efflux from macrophages. Biochem Biophys Res Commun, 296:1051-7.

[10] Herbst KL, Amory JK, Brunzell JD, Chansky HA, Bremner WJ. (2003). Testosterone administration to men increases hepatic lipase activity and decreases HDL and LDL size in 3 wk. Am J Physiol Endocrinol Metab, 284:E1112-8.

[11] Haddad RM, Kennedy CC, Caples SM, Tracz MJ, Bolo ña ER, Sideras K, et al (2007). Testosterone and cardiovascular risk in men: a systematic review and meta-analysis of randomized placebo-controlled trials. Mayo Clin Proc, 82:29-39.

[12] Ruige JB, Mahmoud AM, De Bacquer D, Kaufman JM (2011). Endogenous testosterone and cardiovascular disease in healthy men: a meta-analysis. Heart, 97:870-5.

[13] Grossmann M, Thomas MC, Panagiotopoulos S, Sharpe K, Macisaac RJ, Clarke S, et al (2008). Low testosterone levels are common and associated with insulin resistance in men with diabetes. J Clin Endocrinol Metab, 93:1834-40.

[14] Traish AM, Saad F, Guay A (2009). The dark side of testosterone deficiency: II. Type 2 diabetes and insulin resistance. J Androl, 30:23-32.

[15] Tirabassi G, Gioia A, Giovannini L, Boscaro M, Corona G, Carpi A, et al (2013). Testosterone and cardiovascular risk. Intern Emerg Med, 8 Suppl 1:65-9.

[16] Yeap BB, Hyde Z, Almeida OP, Norman PE, Chubb SA, Jamrozik K, et al (2009). Lower testosterone levels predict incident stroke and transient ischemic attack in older men. J Clin Endocrinol Metab, 94:2353-9

[17] Muller M, van den Beld AW, Bots ML, Grobbee DE, Lamberts SW, van der Schouw YT. (2004). Endogenous sex hormones and progression of carotid atherosclerosis in elderly men. Circulation, 109:2074-9.

[18] Lerchbaum E, Pilz S, Grammer TB, Boehm BO, März W, Obermayer-Pietsch B. (2011). High estradiol levels are associated with increased mortality in older men referred to coronary angiography. Exp Clin Endocrinol Diabetes, 119:490-6.

[19] Callou de Sá EQ, Feijó de Sá FC, e Silva Rde S, de Oliveira KC, Guedes AD, Feres F, et al. (2011). Endogenous oestradiol but not testosterone is related to coronary artery disease in men. Clin Endocrinol (Oxf), 75:177-83.

[20] Mohamad MJ, Mohammad MA, Karayyem M, Hairi A, Hader AA. (2007). Serum levels of sex hormones in men with acute myocardial infarction. Neuro Endocrinol Lett, 28:182-6.

[21] Barud W, Palusinski R, Beltowski J, Wojcicka G, Myslinski W, Grzybowski A, et al. (2010). Relation between markers of inflammation and estradiol in older men. Med Sci Monit, 16:CR593-7.

[22] Boyle JJ. (1997). Association of coronary plaque rupture and atherosclerotic inflammation. J Pathol, 181:93-9.

[23] Tivesten A, Vandenput L, Labrie F, Karlsson MK, Ljunggren O, Mellström D, et al. (2009). Low serum testosterone and estradiol predict mortality in elderly men. J Clin Endocrinol Metab, 94:2482-8.

[24] Zmuda JM, Cauley JA, Kriska A, Glynn NW, Gutai JP, Kuller LH. (1997). Longitudinal relation between endogenous testosterone and cardiovascular disease risk factors in middle-aged men. A 13-year follow-up of former Multiple Risk Factor Intervention Trial participants. Am J Epidemiol, 146:609-17.

[25] Cohen PG (2008). Obesity in men: the hypogonadal-estrogen receptor relationship and its effect on glucose homeostasis. Med Hypotheses, 70:358-60.

[26] Corona G, Rastrelli G, Monami M, Guay A, Buvat J, Sforza A, et al. (2011). Hypogonadism as a risk factor for cardiovascular mortality in men: a meta-analytic study. Eur J Endocrinol, 165:687-701.