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Case Report

Surgical Castration for the Late Development of Resistance to Medical Castration with LHRH Agonists and Antagonists in Castrate-Resistant Prostate Cancer

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Abstract

Acquired resistance to GNRH agonists or antagonists used for the induction of medical castration for the treatment of metastatic prostate cancer has been rarely reported. To date, the mechanism(s) behind the development of apparent resistance to these agents has yet to be adequately defined while the impact of this refractoriness may possibly be detrimental even in Castrate-Resistant Prostate Cancer (CRPC). Here we describe two men with CRPC who were compliant with their GNRH agonist and who had documented low testosterone levels for years. They then developed rising testosterone levels despite documented continued receipt of these agents. Switching to the pure LHRH antagonist, degarelix, did not improve the testosterone suppression. Of interest, repeated determinations of luteinizing hormone were undetectable in both men suggesting the apparent resistance was not at the level of the hypothalamic-pituitary axis. They did not have elevated Beta-HCG, prolactin or estrogen levels. The testosterone levels also did not respond to abiraterone given for their CRPC nor did they ever have sterile abscesses which have been associated with resistance to LHRH agonists. They therefore underwent surgical castration with bilateral orchiectomy and their testosterone levels returned to appropriate castrate levels again suggesting that the failure of medical castration was not due to androgen production by the tumor cells but rather by the gonads. Understanding the endocrine mechanism for this failure remains unclear but the response to surgical castration suggests it is at the level of the gonads. These cases and others support the continued checking of testosterone levels while on long term medical castration agent since resistance can occur after many years of good control. Then, surgical castration becomes the treatment of choice.

Keywords: Surgical Castration; LHRH Agonist Resistance; LHRH Antagonist Resistance; Medical Castration Resistance; Resistant Prostate Cancer; Endocrine Therapy Resistance; Prostate Cancer Resistant To Endocrine Therapy

Introduction

Androgen-Deprivation Therapy (ADT) in the form of castration has been the mainstay of therapy for prostate cancer since the 1940s [1-5]. The goal of ADT is to reduce gonadal androgens to castration levels whether applied surgically with bilateral orchiectomy or medically via gonadotropin receptor- blockage using either LHRH agonists or antagonist (Figure 1). ADT typically only works for a limited time before prostate cancer cells find a way of surviving despite castration serum levels of testosterone, the prostate cancer cells may survive on low levels of androgens produced by the adrenal glands or may actually produce their own androgens [6-8]. They may also survive by becoming completely independent of androgen stimulation [9-11]. Prostate cancer at that juncture has become castration resistant. Even in CRPC, castration therapy should be continued since many of the clones remain sensitive to castration such that stopping it and allowing testosterone levels to rise can result in flares of disease [12]. It has been demonstrated that incomplete testosterone suppression has been associated with increased biochemical failure rates and metastases with worse survival [13]. Previous case reports reported a correlation between LHRH analogues resistance and formation of sterile abscesses or inflammation at sites of LHRH analogue injection which apparently interfere with absorption of the drug from the injection site [14]. However, other reports noted LHRH resistance despite absence of any sterile abscess with goserelin [15], and that resistance developed shortly after initiation of therapy with the second 3-month injection despite the sharp initial response in terms of serum testosterone level and PSA level as well. Many oncologists stop monitoring testosterone levels after levels of testosterone post initiation of medical castration have attained castrate levels. The previous case-reports and our experience suggest that testosterone levels should be monitored regularly in patients on medical castration with GNRH agonists or antagonists since resistance to these drugs can occur either early or late. The mechanism for this apparent failure of these agents to adequately suppress testosterone after years of control has not been elucidated adequately to date but does respond to surgical castration. Here we present 2 cases of men with advanced prostate cancer who developed rising testosterone levels despite regular receipt of these agents which had worked previously.

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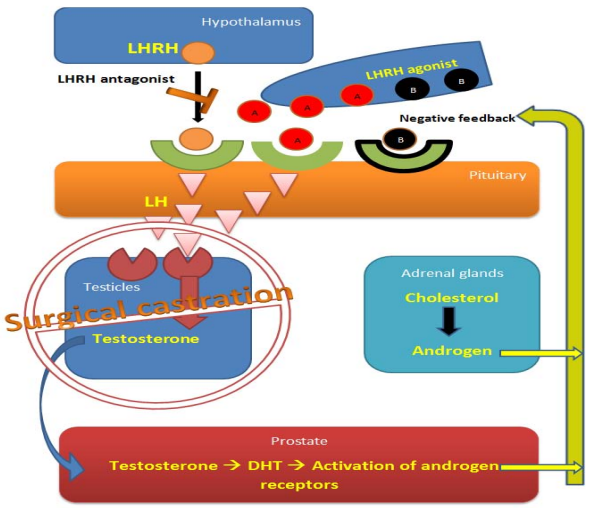

Figure 1: Physiology of the hypothalamus pituitary testes axis.

Some endocrine testing were performed trying to uncover a defect responsible for this breakthrough and in both cases the problem resolved with surgical castration.

Case Reports

Case 1

The first patient is an 85year old gentleman who was originally diagnosed with BPH in 1994 with an elevated PSA. He underwent trans-urethral resection of the prostate and pathology was negative for malignancy. He started having a rapidly rising PSA late in 2004 up to 35. His bone scan on Nov. 5th, 2004 showed one solitary area of uptake in 10th left rib worrisome for metastatic focus. It was consistent with a sclerotic area on a plain film. Biopsy confirmed adenocarcinoma of the prostate. He was placed on Leuprolide depot at diagnosis in Nov. 2004 and his PSA declined and reached a nadir level of 2. His PSA and bone scan remained stable till May 2007 when the 10th rib lesion appeared worse on bone scan but no additional lesions were noted; PSA at that time was slightly higher at 5.6 and he was asymptomatic. He continued the leuprolide depot injections. He presented with gross hematuria in Nov. 2006 and underwent TURBT x 2 where he was found to have an incidental superficial bladder transitional cell carcinoma and he has been without any evidence of TCC recurrence ever since on regular surveillance.

Two months later in Jul. 2007, his bone scan revealed new rib metastatic foci and his PSA increased to 7.8. (See Table 1) His DEXA scan was consistent with osteoporosis. He was then diagnosed as having CRPC and so was started on high dose Bicalutamide as first line treatment in addition to his LHRH agonist and he was also started on monthly Zolidronic acid for the metastatic bone disease. On therapy, his PSA declined to 3.4. Testosterone was documented then to be in a castrate range at< 15 ng/dL on Apr. 1st, 2008 and a CT urogram revealed a large lobular prostate. PSA then started to rise slowly again. Bicalutamide was therefore stopped trying to induce an anti androgen withdrawal response; PSA, however only dropped from 5.52 to 5.35 with Bicalutamide withdrawal and it began to raise again consistent with disease progression. Bone scan and CT scans in Jul. 2008 were done in lieu of rising PSA and they were both stable. He was then started on Ketoconazole and hydrocortisone as the next second line hormonal therapy. The PSA dropped on ketoconazolefrom 7.06 to 1.66 over 9 months and remained low. Zolidronic acid was stopped after 2 years of monthly treatments. He had another TURP meanwhile for large volume prostate with symptoms of outflow obstruction. Of interest, the prostate tissue obtained from this TURP was negative for cancer consistent with an excellent response to ketoconazole. After this good control, his PSA started to rise slowly again, and therefore Ketoconazole was discontinued. Denosumab 120 monthly with Ca and vitamin D were started. Sipuleucel-T was offered to him but he declined and therefore abiraterone was started with prednisone late in Apr. 2013 which he tolerated very well. His PSA dropped from 6.35 in Apr. 2013 to 3.58 in May 2013. However, his testosterone level was noted to be 80 on May 30th, 2013 and was 50 on Jun. 6th, 2013. It had been very low for years as noted. Thus, he was switched from Lupron to degarelix "Firmagon" in Jun. 2013. However, no improvement in testosterone level was noted as his testosterone level remained between 50-105 between Jul. 2013 and Feb. 2014 (Table 1),

Table 1: PSA and Testosterone levels for Patient of Case 1.

Date	PSA	Serum testosterone	BMI
Jan. 18th, 2012	3.09	< 15	28.36
Apr. 18th, 2012	3.68	10	28.46
Jun. 14th, 2012	2.42	< 5	28.46
Aug. 2nd, 2012	3.22	< 5	28.4
Oct. 5th, 2012	4.33	< 5	28.4
Nov. 30th, 2012	4.91	7	28.4
Jan. 7th, 2013	5.83	< 5	28.4
Feb. 7th, 2013	5.51	< 5	28.8
Apr. 2nd, 2013	6.35	< 5	28.98
May 31st, 2013	3.58	80	27.75
Jun. 6th, 2013	3.58	50→ so luprolide was changed to degarelix	27.75
Jul. 7th, 2013	3.2	105	27.99
Oct. 4th, 2013	2.89	70	27.56
Dec. 6th, 2013	2.95	63	27.56
Feb. 4th, 2014	4.78	50	27.44
surgical castration Mar. 10th, 2014 with bilateral orchiectomy			27.28
Apr. 24th, 2014	4.82	< 5	27.44
June 20th, 2014	3.88	< 5	27.44

Table 2: PSA and Testosterone levels for Patient of Case 2.

Date	PSA	Serum testosterone	BMI
Mar. 8th, 2012	13.25	16	25.45
Jul. 9th, 2012	16.84	16	25.17
Aug. 16th, 2012	22.4	63	25.04
Sep. 14th, 2012	22.8	70	25.71
Nov. 6th, 2012	21.69	31	25.71
Dec. 12th, 2012	25.59	48	25.49
Feb. 26th, 2013	32.57	48	25.64
May 1st, 2013	46.48	100	24.98
May 17th, 2013	36.35	78→ so luprolide was changed to degarelix	24.98
Jul. 25th, 2013	57.61	123	25.68
Sep. 15h, 2013	59.86	Not done	25.26
Nov. 12th, 2013	88.70	48	25.97
surgical castration Nov. 1st, 2013 with bilateral orchiectomy			25.97
Jan. 14th, 2014	97.12	<5	26.13
Mar. 31st, 2014	142.16	12	26.13
May 5th, 2014	151.49	5	24.65
Jun. 2nd, 2014	176.46	<5	24.4
Jul. 1st, 2014	264.26	Not done	24.01

and therefore surgical bilateral orchiectomy was recommended. In an effort to understand the mechanism behind this surprising aberration we did some laboratory investigations. He never had any problems with his injections and there were no clinical or radiographic findings to suggest the development of sterile abscesses at the injection sites. His LH was low < 0.22mIU/ml in Dec. 2013 and also in Feb. 2014 (normal range is 1.14-8.75mIU/ml). His prolactin, estrogen and HCG serum levels were normal. In the interim, he had more urinary output obstruction and a temporary urinary catheter was placed and was treated and resolved with flomax. On Mar. 10th, 2014, he underwent rigid cystoscopy with another transurethral resection of the prostate and also had bilateral scrotal orchiectomy under spinal anesthesia. His surgical pathology revealed high grade prostatic adenocarcinoma in bladder neck whereas his testicles showed global atrophy. On his first post-op visit on Apr. 24th, 2014, his PSA was stable on abiraterone at 4.82. His testosterone did come down to < 15 by Apr. 2014; free testosterone was < 1. He has continued to be stable clinically and by Jun. 2014 his PSA dropped again on continued abiraterone to 3.88 suggesting the surgical castration may have led to better PSA control.

Case 2

This is an 83 year old gentleman with history of spine degenerative joint and disk disease who had laminectomy complicated with osteomyelitis in 2010. On routine follow up imaging of the spine in Sep. 2011, he was noted to have multiple sclerotic lesions involving the spine worrisome for metastatic disease. He underwent biopsies of some of the lytic lesions on Oct. 17th, 2011. The pathology revealed an adenocarcinoma consistent with prostatic carcinoma by immunohistochemistry. Bone scan showed additional multiple osseous lesions involving ribs and spine. His initial PSA at that time was elevated at 16.5. His last PSA, checked several years prior, was about 4 which had been stable compared with prior years. Therefore, he was seen by urology and medical oncology and was started on Leuprolide depot injection and bicalutamide as total androgen blockade in Oct. 2011. He also began denosumab for the osseous metastatic disease in Feb. 2012. His PSA was suppressed until Jul. 2012 when it rose to 16.84 while still in castrate state by measuring testosterone level consistent with the development of CRPC. The patient had multiple significant medical problems including cardiomyopathy with intermittent bouts of CHF. Bicalutamide was stopped on Jul. 10th, 2012 and we hoped for an anti-androgen withdrawal response. Unfortunately, his PSA continued to climb and he thus did not respond to bicalutamide withdrawal (see Table 2). Sipuleucel-T could not be administered due to cardiac comorbidities particularly with leukapheresis requirement. He was then started on abiraterone with low dose prednisone on Aug. 16th, 2012. He underwent CT scans on Feb. 25th, 2013 which showed new bladder lesions and disease progression in bones. He was then re-evaluated by urology with cystoscopy and was found to have new bladder cancer. He underwent Transurethral Resection of the Bladder Tumor (TURBT) on Mar. 26th, 2013. Surgical pathology revealed high grade papillary Transitional Cell Carcinoma (TCC), Ta G4 and was treated with BCG treatments. His PSA had been slowly rising between 16 and 32 till May 2013 when his PSA rose from 32.57 to 46.48. His testosterone level was noted to be 100 despite having had Leuprolide (the 3 month depot) 2 months prior and despite being on abiraterone and prednisone as well. Previous testosterone levels while on abiraterone were running about 48, much higher than expected with Leuprolide and abiraterone use. Therefore, on May 17th, 2013 Leuprolide was changed to degarelix in an effort totry to obtain adequate testosterone suppression, while abiraterone was continued. His testosterone level continued to be high on degarelix as well as it rose to 123 (Table 2). Therefore, it too was stopped on Sep. 19th, 2013 and surgical castration with bilateral orchiectomy was recommended. LH levels were low and no other endocrine abnormalities were found. This surgical castration was done along with his surveillance cystoscopy on Nov. 1st, 2013. The testicles showed simple atrophy. His post-op testosterone level came down to < 5 and have remained appropriately low, however, his PSA continued to rise as it rose from 88.7 in Nov. 2013 to 97.1 in Jan. 2014 to 142.16 in Mar. 2014 consistent with continued disease progressionon abiraterone. Therefore his abiraterone was stopped and was started on Enzalutamide on Dec. 15th, 2013. His CT scans and bone scan in Jan. 2014 were consistent with stable disease. The alkaline phosphatase started to rise suggestive of worsening bone disease. His PSA rose further to 151.9 in May 2014

and therefore repeated CT scans were done which revealed stable osseous metastatic disease and patient elected to start Radium 223 on May 8th, 2014; he was having some increasing bone discomfort at the time. He received 3 Radium doses so far to the date of writing this publication but his PSA continued to rise despite being constantly in the surgical castration state with testosterone level <5 since the bilateral orchiectomy. He remains pain free however at the current time. The plan is to offer Docetaxel post Radium for disease progression.

Discussion

We described two men who had initial long term excellent testosterone suppression on LHRH agonists but later developed rising then persistently higher non-castrate testosterone levels despite continued receipt of these agents. We tried to explore the mechanisms for this late failure. Both men had repeatedly low LH levels suggesting the agents were indeed working at the pituitary to suppress production. There were no sterile abscesses noted which have been reported to impair absorption of the drugs at the injections sites and the low LH levels suggested that the drug was indeed absorbed and working at least at the level of the pituitary so mechanisms such as alternation in the GNRH receptor or antibodies interfering with GNRH drugs should not be operant. Likewise, there were no other abnormalities in estrogen, BHCG or prolactin noted. Changing from the GNRH agonist, leuprolide to the pure GNRH antagonist, degarelix, had no impact at all. Surgical castration, however, did result in return of testosterone levels to castrate levels. This suggested to us that the source of resistance to these drugs was at the level of the gonad. The removed testicles just showed atrophy on pathologic analysis. We postulated that in a state of chronic low LH levels the gonads may become independent of LH completely, or the receptors for LH in the gonads may become hypersensitive to even small amounts of LH; and this, in either case, results in increased testosterone production. Another possibility to consider would be the presence of LH-like peptide or even beta-HCG driving the gonadal production of testosterone. Beta-HCG is known to act on the LH receptors in the testicles and therefore can stimulate testosterone secretion. It is possible that some prostate cancer cells may start secreting beta HCG (or some other LH-like substances) in a paraneoplastic fashion that can stimulate LH receptors in testes. Our patients had normal beta HCG determinations but we cannot rule out the presence of LH or HCG like peptides which are functional but not measured. Surgical castration would also work if this was the mechanism as well. We also considered that the results could have been due to a laboratory artifact due to the cross reactivity of the testosterone assay with other androgen-like molecules. We wondered if the abiraterone, which has steroidal hormonal structure would do that. We thought this unlikely, however since we have many men on LHRH drugs and abiraterone in whom we regularly monitor testosterone levels and have only observed this phenomenon rarely and also because the tester one levels dropped post castration but while still on abiraterone. Likewise, in clinical studies with abiraterone, testosterone levels were documented to be very low consistent with its mechanism of action [16,17]. Whether the transient non-castrate levels of testosterone noted in our patients had an additional adverse effect in the course of their already CRPC is debatable but Patient 1 did have a lower PSA coincident with a lower testosterone after surgical castration. Synthetic LHRH analogues have been used to provide medical castration in prostate cancer with progression after surgical prostatectomy or prostatic radiotherapy and with metastatic disease at diagnosis as in the men described here. Historically, the goal of medical castration is to achieve serum testosterone levels less was than 50 ng/dl (<1.7nmol/L) [18]. However, Testosterone levels >32 ng/dL (>1.1 nmol/L) are currently considered no longer fully suppressed according to a recent report [19]. With surgical orchiectomy, testosterone levels should reach <20 ng/dL (< 0.7 nmol/L) [20]. LHRH agonists and antagonists has been an excellent non-invasive therapeutic option for castration and appear equally effective in comparison to surgical orchiectomy in clinical outcomes. However, in about 13%-21% of patients, testosterone levels with LHRH agonist may not achieve the surgical orchiectomy testosterone levels and indeed higher testosterone levels have been associated with increased levels of PSA and an increased death rate in patients with CRPC [13,20]. On the other hand, only 10% of patients who undergo surgical castration will fail to achieve total testosterone level less than 20 ng/dL (<0.7 nmol/L) [21]. Previous studies have shown that up to 12% of prostate cancers patients fail to have testosterone level to less than 50 ng/dl (<1.7 nmol/L) [22-24]. A report of 451 patients showed that percentage was 11% [25]. In 2010, the largest study to date, presented a population of 2196 patients which confirmed that breakthrough can occur with lower degrees of testosterone suppression per patient of 3.4% ≥ 50 ng/dL (≥1.7 nmol/L) and 6.6% ≥ 32 ng/dL (≥1.1 nmol/L) using testosterone assays that have been shown to be more accurate at low levels [26]. By its effect on both adrenal and tumoral hormonogenesis, abiraterone allows clinicians to bring serum testosterone levels to less than 20 ng/dl and in theory help some of those patients who may be incompletely suppressed by LHRH analogues. Of note, it did not do so in our patients on the drug suggesting they still had gonadal production of male hormones not suppressed by abiraterone. LH expression in prostate cancer tissues has been associated with poor prognosis, while FSH has been shown to stimulate prostate cell growth in hormone-refractory prostate cancer cell lines. In addition, there is evidence that high testosterone levels are associated with poor prognosis [19,27]. Patients with a higher than castration levels of testosterone at 6 months experienced a 1.3-fold greater risk of cancer-related mortality (95%CI 1.05-1.69; p< 0.05) [13]. GnRH and its receptors are present in multiple other tissues in addition to the pituitary gland. They are found in prostate, ovaries, breasts, placenta and endometrium. Testosterone breakthrough risk was studied in 2196 patients from the British Columbia Cancer registry data set which revealed the risk of testosterone breakthrough to >1.1 nmol/L (>32 ng/dL) is 6.6%, whereas is it 5.4 % for level > 50 ng/dL (>1.7 nmol/L) per patient course. On the other hand, that risk is 5.4% and 2.2% respectively per LHRH agonist injection. Recurrence of the breakthrough decreases the Prostate cancer-free survival from 73% to 58% [26]. Expression of LH and Beta-HCG in prostate cancer tissues is consistent with poor prognosis and entitles higher risk for metastatic disease. LH up-regulates enzymes and genes responsible for sex steroids production via prostate cancer cells [28]. This can lead to an important role of LH-receptor signaling in prostate cancer in becoming castration resistant. However, LH levels were not noted to be higher in prostate cancer when compared with those levels in benign prostatic hypertrophy or even when those levels are compared between

localized and locally advanced prostate cancers [29-31]. Furthermore, this expression of either LH or beta-HCG could be responsible for more aggressive malignant evolution of prostate cancer cells by changing their shapes, migration, invasiveness and adhesiveness as well [32]. Differently, FSH was noted in previous research to be higher in prostate cancer than in BPH. It was also found to be even higher in locally advanced prostate cancer than in localized prostate cancer [29,33]. FSH stimulates prostate cell growth in castration resistant prostate cancer cell lines [34]. In absence of prostate cancer, FSH synthesis and release can be suppressed by a protein produced by prostate gland called PIP (Prostatic In hibin Peptide). This PIP production is suppressed in prostate cancer. Low PIP allows more FSH to be synthesized and released and in turn more prostate cancer cell growth [35-37]. Our patients had low LH levels suggesting that the GNRH agonists and antagonists used were effective in suppressing this intermediary hormone but not the testosterone production at the level of the gonads. No published data explaining the reason for treatment failure with LHRH agonists or antagonists exist to the best of our knowledge. Similarly, no identified risk factors for developing LHRH therapy resistance have been described. Our experience suggests that failure of one LHRH agonist or antagonist to suppress testosterone to castration level reflects a general resistance to LHRH therapy rather than only resistance to the agent in question. Many oncologists stop monitoring testosterone level after reaching first castrated level of testosterone post initiation of medical castration. The two cases we presented here stress the necessity of monitoring testosterone level periodically while on endocrine therapy but particularly with disease progression. Patients who develop sterile abscesses or inflammation at sites of depot injections should have close monitoring of their testosterone level. Resistance to GNRH agents appears to be at the level of the gonads and bilateral surgical orchiectomies succeed in getting very low testosterone levels in men who have failed all different forms of castration from LHRH agonist, LHRH antagonist, androgen receptor inhibitors, and CYP 17 hydroxylase inhibitors. Evidence suggests that this may benefit patients even in the castrate-resistance phase of the disease therapy.

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