The Overactive Bladder Controversies in the Pathophysiologic Basis of Unstable Detrusor Contraction

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Introduction

The concept of the overactive bladder was first introduced by Bates in the 1960’s as a description of an observation of the loss of the ability to inhibit normal detrusor activity (Bates 1971). Although emphasizing that the term did not imply a pathology, he acknowledged it to be of considerable importance in clinical practice, mainly because of its possible role as the cause of undesirable symptoms post surgery for incontinence.

Clinical Relevance of the Condition

Since that time, there has been increasing interest in the condition, not only in the context cited by Bates. Symptoms characteristic of an overactive bladder (OAB) have been seen in a growing number of clinical cases. In 1998, the Asia-Pacific Continence Advisory Board conducted a multinational institution-based questionnaire survey to determine the prevalence of incontinence and voiding disorders among Asians (Lapitan 1999). According to this report, 53 percent of the study population manifested symptoms of frequency, urgency or urge incontinence, of which, 25 percent were bothered significantly by these symptoms and 21 percent sought help. This translates to approximately 11 – 12 percent of the population being potential patients suffering from the overactive bladder. The APCAB report parallels the result of the SIFO group that surveyed 6 European countries and found the prevalence of OAB symptoms ranging from 12 to 22 percent across different age groups (Milsom 1999).

Symptoms of the overactive bladder are also seen in a wide range of clinical conditions such as neurologic diseases including central nervous system disorders, spinal cord pathologies, and peripheral neuropathies, bladder outlet obstruction, and genitourinary tract infection and inflammation.

Although the condition of the unstable bladder in itself is not life-threatening, it leaves one with such a condition a dreadful life to live. Komaroff and co-workers (Komaroff 1996) compared the quality of life scores of diabetics, OAB patients and normal individuals. They found that patients suffering from OAB symptoms had lower scores in all aspects except bodily pain and general health compared to diabetics.

The overactive bladder is of the most difficult and frustrating conditions to manage in the urologic clinic. As cited by Bates, a significant cause for post-surgical morbidity is the presence of OAB. Jorgensen and coworkers (Jorgensen 1988), in a prospective comparative study of 80 females who underwent surgical correction of stress incontinence found higher failure rates among those with overactive bladders. Treatment of associated conditions, which are often regarded as the main cause of the overactivity of the bladder, does not always mean resolution of its symptoms. For example, only 60 percent of BPH...
patients with OAB symptoms will have stable bladders post-TURP. Finally, reviewing the reports of the various therapeutic modalities being studied for the overactive bladder at present shows that the efficacy of any one treatment regimen is 80% at best.

Perhaps the most important issue in the management of bladder overactivity is that etiology-based treatment is not yet possible because the exact pathophysiologic mechanism behind it is still not fully understood. What is wrong with the bladder? The question still remains unanswered.

Much work has been done in the past two decades attempting to reveal the underlying pathology in the development of the overactive bladder. Many theories have been proposed based on the mechanisms that work behind the micturition cycle, particularly during the storage phase and how the pathologic state render the bladder unstable.

**Detrusor Mechanisms for Storage in the Normal Bladder**

The micturition cycle is an alternating sequence of storage and elimination, i.e., filling and voiding. The overactive bladder is basically a problem in the filling or storage phase caused by a pathologic detrusor.

In the normal state, several detrusor mechanisms are at work during storage. These include: (1) the micturition reflex, the neural circuitry controlling the bladder, is on the “off” mode during storage, (2) the detrusor smooth muscle is rendered stable, and (3) extracellular matrix components, mainly elastin and collagen, possess properties that render the bladder tissue compliant.

**Theories on the Pathophysiologic Mechanisms of the Overactive Bladder**

In the overactive bladder, these mechanisms are proposed to be abnormal. There is uncontrolled and uninhibited switching of the micturition reflex to the “on” mode. The normally stable detrusor muscle is rendered unstable by some structural and biochemical changes so that inappropriate contractions appear. The extracellular matrix components have undergone some transformation so that the bladder becomes noncompliant.

**The Neurogenic Theory**

Foremost among the theories currently being studied are the neurogenic and the myogenic paradigms for the overactive bladder. The principal proponents of the neurogenic theory are Dr. William de Groat and Dr. Christopher Fry.

According to the neurogenic theory, the overactive bladder is caused by a partial uncontrolled on-off mechanism in the nervous system so that there is a premature activation of the micturition reflex. This may be brought about by a failure or the abnormal functioning of any of the components of the micturition reflex circuitry.

**The Micturition Reflex in the Storage Phase**

The neural circuitry of the micturition reflex is made up of 4 components: (1) spinal afferent neuron, (2) spinal efferent neurons, (3) spinal interneurons, and (4) central pathways. In the normal state, during the storage phase, the spinal afferent pathway is subserved by pelvic nerve afferents that transmit low-level vesical activity. These nerves are mainly of the alpha-sigma (Ao) small myelinated fibers which are triggered by tension receptors in the detrusor tissue. Large myelinated fibers, also known as C-fibers are also found among afferent nerves. These fibers originate from pain and thermoceptors and are of a normally high threshold level so that they are generally inactive in the normal micturition reflex.

The spinal efferent pathways include (1) the pudendal (somatic) nerve causing external sphincter contraction, (2) the hypogastric (sympathetic) nerve causing the internal sphincter contraction, detrusor (passive) relaxation, and ganglionic inhibition, and (3) sacral parasympathetic pelvic nerve efferent outflow which is in an inactive mode during the storage phase. It is believed that the quiescence of the parasympathetic efferent is the crucial and most significant factor determining the overall status of the lower urinary tract during the filling phase. Such inactivity is mainly the result of the inhibitory signals generated by the medial and frontal lobes and basal ganglia and transmitted through the central pathways and spinal interneurons.

The neurogenic basis of the overactive bladder proposes that there is an abnormality in the reflex. This may manifest as (1) increased or altered afferent
input from the lower urinary tract, (2) increased efferent signals, and (3) loss of central inhibition (de Groat 1997).

Changes in the Afferent Pathway

Kruse and co workers (Kruse 1995) performed anatomic tracer studies in the chronic spinal animals and found that there was an increase in the diameter of afferent neurons compared with normals. The increase in size was postulated to be associated with sprouting of afferent axons.

The hypertrophy of bladder afferents was accompanied by increased levels of nerve growth factor (NGF) in the bladder (Steers 1991). This increased production of NGF results from direct mechanical deformation of the smooth muscle or the influence of cytokines on bladder tissues such as those seen in bladder outlet obstruction, infection and inflammation.

While it is unclear what type of fibers make up these new axons, there is evidence that these are of the C-large myelinated type. Indirect proof of this fact comes mainly from the immunohistochemical studies by de Groat’s group. They found that there is an increase in the VIP immunoreactivity in the overactive detrusor tissue signifying a higher load of C-fibers. Such was also demonstrated in the spinal cord where there was a wider distribution of the afferent terminals in the later dorsal horn of paraplegic cats (Thor 1986).

Aside from an increase in the number and size of afferents, there is believed to be an unmasking of the normally silent C-fiber mediated afferent pathway, as well as a change in its properties. Following spinal cord injury in the cat, reorganization of the reflex connections occur such that C-fiber afferent evoked reflexes are facilitated and enabled to respond to bladder distention. Maggi (Maggi 1997) suggested that such activation of the C-fibers by stretching may be mediated by the release of prostanoids by the vesical mucosa. However, it is still unclear whether this contributes to the pathogenesis of the overactive bladder.

Turning to the clinics to prove these findings in basic research, studies have shown that administration of capsaicin, a C-fiber neurotoxin was associated with the elimination of the hyperreflexic contractions of the bladder.

Loss of Central Control

Findings on the central control of the micturition reflex have been based on animal lesion studies whereby neural transactions and lobotomies performed attempted to replicate various voiding conditions, retrograde virus tracings to establish pathways and connections and in depth analysis of various clinical cases.

As indicated earlier, in the normal state, tonic inhibitory signals to the spinal cord micturition center are sent out from the brain. The principal inhibitory neurotransmitters are identified to be gamma aminobutyric acid (GABA), serotonin, and dopamine, to a certain extent.

Lesion models in animal studies have identified the medical frontal lobes of the cerebral cortex, basal ganglia, posterior and medial hypothalamus and the paraventricular nucleus as the origin of inhibitory impulses controlling the micturition reflex in the storage phase. Strong linkage between impaired temporal orientation and urge incontinence, both of which are associated with the medial frontal lobes (Griffiths 1994) and the underperfusion of the right frontal lobe cortex on single-photon emission in patients with overactive bladder (Griffiths 1997) confirm these findings among humans. It is a common observation that Parkinson’s disease, which affects the basal ganglia, is associated with OAB. Destruction of dopamine neurons produces animal Parkinson’s model manifesting all signs of parkinsonism, including the overactive bladder (Albanease 1988).

Changes in the Efferent Pathway

More noteworthy than altered afferent neurons and loss of central control in the neurogenic theory for the overactive bladder is the concept that there is significant transformation in the efferent pathways. One of those changes is the appearance of purinergic, ATP-mediated, atropine-resistant contractions.

In the normal bladder, smooth muscle contraction is brought about by stimulation from
acetylcholine-releasing nerve endings. However, in the overactive bladder, contractions brought about by ATP stimulation appear (Bayliss 1999). Using single detrusor muscle cell studies, this UK group of C Fry attributed the increased concentration of ATP reaching the myocyte to: (1) decreased hydrolysis of ATP at the synaptic cleft, (2) increased ATP released from the terminal nerve, and (3) decreased relative concentration of acetylcholine due to its increased hydrolysis. Further studies of the group (Wu 1999) demonstrated that the purinergic response in the overactive bladder is a consequence mainly of changes in the extracellular handling of the released ATP (reason 1).

There is also increased sensitivity to adrenergic stimulation in OAB. Stable bladder conditions demonstrate a predominance of beta-adrenergic receptors in the detrusor mediating relaxation and sparse alpha 1d adrenergic receptors in the spinal cord and ganglia, which is facilitatory to the voiding reflex, and in the detrusor causing contraction. In OAB, there is a shift in alpha-receptor predominance in the detrusor (Restorick 1989) and an increased density on cholinergic neurons, vesical ganglia and spinal cord pathways (Andersson 2000).

The Myogenic Theory

The myogenic theory as the basis for the overactive bladder has been promoted by works of Elbadawi and the Oxford Continence Group of electron microscopies, electrophysiologic studies of muscle biopsies smooth muscle strips from unstable detrusors. The main assertion of this theory is that detrusor overactivity is caused by an overall reduction in the activity of the efferent neurons which subsequently induces alterations in smooth muscle properties. The intrinsic changes in the detrusor smooth muscle cell ultrastructure and property lead to increased excitability and increased ability of the activity to spread between the cells.

The altered ultrastructure of the overactive detrusor muscle cell was first described by Eldabawi in 1993 (Elbadawi 1993). He noted changes in the cell-to-cell attachments through loss of normal intermediate gap junctions and appearance of protrusion and ultraclose abutments. Such morphology allows enhanced electromechanical coupling of the detrusor muscle cells so that there is “syncytium-like” propagation of electrical impulses. This is in contrast to the normal state wherein focal areas of activity in the bladder dissipates and do not result in the contraction of the whole organ.

A review by Brading of the Oxford Continence Group (Brading 1997) presented evidence from in vitro analysis and immunohistochemical staining of detrusor muscle strips comparing normal and unstable bladders further proposed that the cellular changes are associated with patchy denervation. Cellular hypoxia has been implicated as the principal cause for such denervation and structural alteration (Fry 1997, Azadzoi 1999).

Elbadawi has proposed that the enhanced cell-cell coupling effected by the ultrastructural alterations as the final common pathway or mechanism in the development of detrusor overactivity. For involuntary contractions to occur in the different clinical conditions, whether it is primarily neurologic or bladder outlet obstruction in nature, the transformation of the bladder into a syncytial contractile tissue is crucial.

Although not included in the discourse by the proponents of the myogenic theory, the finding of altered smooth contractile proteins in the overactive bladder is in keeping with the concept of the change in the cellular ultrastructure. In a review of the smooth muscle physiology by Zimmern and coauthors (Zimmern 1996), they presented evidence on the predominance of the higher molecular weight (SM1) isoform of the myosin high-molecular weight chain (MHC) in the overactive bladder. This dedifferentiation from the normal SM2-predominant MHC is similar to that seen in the fetal bladder. The significance of such transformation is in the cell’s expression of extracellular matrix (see page 5).

They also presented results that show altered form of caldesmon in the overactive bladder. Caldesmon binds with calmodulin and actin to modulate smooth muscle contraction by inhibiting the acto-myosin MgATPase (this enzyme allows further latching of myosin to actin which is the essence of the smooth muscle contraction). In the normal state, the h-caldesmon form predominate but in detrusor overactivity, caldesmon is found to be in the l-form, which do not have the same inhibitory capability.
Changes in the Extracellular Matrix

The amount and type of extracellular matrix surrounding the myocytes in the bladder is important in maintaining the appropriate environment of signal transmission between cells and compliance. An increase in the amount of extracellular matrix in the bladder wall leads to a decrease in compliance. The dedifferentiation of the detrusor smooth muscle in the overactive bladder is implicated in the increased expression and production of collagen that compromises its stability and modifies distensibility and contractility. (Zimmern 1996)

Summary

Integrating all the presented evidence on the possible pathophysiologic basis of the overactive bladder, the following flow of events for its development is proposed (see figure below). It is probable that all theories contribute together to the overall manifestation of detrusor overactivity and that one mechanism affects the other. A clearer understanding of the relationships between events remains to be subject of intense research.

![Flowchart diagram of the pathophysiology of overactive bladder](https://example.com/pathway_diagram.png)
References


A Randomized, Controlled Trial of Pretreatment with Finasteride in Patients with Benign Prostate Hyperplasia Undergoing Transurethral Resection of the Prostate: Its Effects on Perioperative Bleeding and Microvessel Density

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Objectives: (1) To evaluate the expression of prostatic microvessel density in patients with benign prostatic hyperplasia (BPH) treated with finasteride among Filipino patients. (2) To evaluate the effects of finasteride in perioperative bleeding in patients undergoing transurethral resection of prostate for BPH. Materials and Methods: Twenty (20) patients scheduled to undergo transurethral prostatic surgery for benign disease were randomized to pretreatment of finasteride 5 mg tablet once a day for 2 weeks before surgery. Perioperative bleeding parameters include serum hemoglobin determination one day before surgery and immediately 6 hours after the surgery and day 1 post-op. Parraffin blocks were sent for special immunohistochemical von Willebrand factor (factor 8) staining and microvessel density were analyzed. Results: There was a significant difference in the mean decrease in serum hemoglobin level from the preoperative level to that measured in the immediate postoperative recovery period (4.2 + 2.30 gm/dL vs 7.4 + 3.63 gm/dL). However, there was no significant difference in the mean decrease in pre-operative serum hemoglobin level compared with the level measured one day after the procedure (8.9 + 8.01 gm/dL vs. 15.20 + 10.04 gm/dL). There was significantly less hemoglobin in the irrigation fluid in the finasteride group than in the control group (1.28 + 1.38 vs 7.92 + 6.34). Mean microvascular density in the finasteride group was 58.00 + 2.50 and in controls, 71.00 + 31.07. Conclusion: Pretreatment with Finasteride 5 mg given daily for 2 weeks in patients with BPH undergoing TURP significantly decreases perioperative bleeding. Finasteride administration also decreases microvessel density in prostatic tissue.

Key words: finasteride, transurethral resection of prostate

Introduction

Several studies have confirmed the benefit of finasteride in limiting hematuria from benign prostatic hyperplasia (BPH). 1 Mechanisms of decreased bleeding, likewise, the expression of growth factors and microvessel density were also evaluated. Finasteride was also prospectively studied in chronic hematuria and was found out to be effective in suppressing hematuria caused by benign prostatic hyperplasia. 2 Similar studies also presented the effectiveness and long term results after finasteride treatment of hematuria in benign prostatic hyperplasia.

Finasteride, a 5-alpha reductase inhibitor, blocks the conversion of testosterone to dihydrotestosterone and is used as treatment for BPH. As a 5-alpha reductase inhibitor, it decreases activity of androgen controlled growth factors responsible for angiogenesis and therefore, theoretically less
prostatic bleeding. Bailey and Foley reported that patients with hematuria have a much higher concentration of blood vessels in the suburothelial prostatic urethra. It also reported that prostatic vessel density in human decreases in response to finasteride. The identification of microvessel density has influenced the understanding of BPH-related hematuria. It has been studied as a possible pathophysiological basis for the significant decrease in BPH-related hematuria experienced by patients treated with finasteride.

Recently, Finasteride has been suggested to decrease bleeding in patients undergoing transurethral resection of prostate. Similar studies by Hagerty, et al. reported that patients undergoing TURP who were pretreated with finasteride had decreased bleeding perioperatively.

Objectives

1. To evaluate the expression of prostatic microvessel density in patients with benign prostatic hyperplasia treated with finasteride among Filipino patients.

2. To evaluate the effects of finasteride in perioperative bleeding in patients undergoing transurethral resection of prostate for BPH.

Materials and Methods

Twenty (20) patients scheduled to undergo transurethral prostatic surgery for benign disease were randomized to pretreatment (A) and non-pretreatment group (B). Ten (10) patients were given finasteride 5 mg tablet once a day for 2 weeks before surgery and the remaining 10 served as controls. Patients were advised and written informed consent were secured inclusion criteria included an indication for transurethral prostate surgery and a prostate size of at least 40 cc. Exclusion criteria were: patients with suspected malignancy, elevated PSA, patients with renal impairment, coagulopathy and those on aspirin treatment.

Perioperative bleeding parameters include: serum hemoglobin determination one day before surgery, and immediately 6 hours after the surgery and day 1 post-op. Blood loss during the surgery was estimated by measuring the hemoglobin concentration in the irrigating fluid used during the operation. A 5 cc aliquot of the total irrigant used was sent to the laboratory for hemoglobin concentration determination.

Paraffin blocks were sent for special immunohistochemical von Willebrand factor (factor 8) staining and microvessel density were analyzed. Analysis of each specimen was performed in a blinded fashion. Microvessel density was calculated by counting the number of positively stained blood vessels on 10 consecutive, nonoverlapping, high power fields within the hyperplastic prostate compartments. Two operating surgeons were also blinded to finasteride administration. Results were analyzed using Student’s t-test.

Results

Twenty (20) patients underwent transurethral resection of prostate of whom 10 received finasteride and 10 served as controls. There was no difference in the 2 groups as to the age and resected prostate weight. There was a significant difference in the mean decrease in serum hemoglobin level from the preoperative level to that measured in the immediate post-operative recovery period (4.2 ± 2.30 gm/dL vs 7.4 ± 3.63 gm/dL). However, there was no significant difference in the mean decrease in pre-operative serum hemoglobin level compared with the level measured one day after the procedure (8.9 ± 8.01 gm/dL vs 15.20 ± 10.04 gm/dL). (Table 1)

Table 1. Patient variable and results.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Finasteride</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age (yrs)</td>
<td>64.7 (57-71)</td>
<td>66.9 (57-78)</td>
<td></td>
</tr>
<tr>
<td>Mean resected tissue (gm)</td>
<td>19.5 (10.32)</td>
<td>19.3 (10-41)</td>
<td></td>
</tr>
<tr>
<td>Mean gm/dL Hgb decrease</td>
<td></td>
<td></td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>a. Immediate</td>
<td>7.4 ± 3.63</td>
<td>4.2 ± 2.30</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>b. Day 1 post-op</td>
<td>15.20 ± 10.04</td>
<td>8.9 ± 8.01</td>
<td></td>
</tr>
<tr>
<td>Mean Hgb level</td>
<td></td>
<td></td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>a. Irritant used</td>
<td>7.92 ± 6.34</td>
<td>1.28 ± 1.38</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>b. Gram resected prostate</td>
<td>0.39 ± 0.27</td>
<td>0.067 ± 0.06</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>Microvessel density</td>
<td>71.00 ± 31.07</td>
<td>58.00 ± 21.50</td>
<td>actual value</td>
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</tbody>
</table>
There was significantly less hemoglobin level in irrigation fluid in the finasteride group than in the control group (1.28 ± 1.38 vs 7.92 ± 6.34) signifying less blood loss. The ratio of hemoglobin loss to the weight of the prostate resected in each group was found to be significant. (0.067 ± 0.06 vs 0.39 + 0.27).

Mean microvascular density in the finasteride group was 58.00 ± 21.50 and in controls, 71.00 ± 31.07. However, this has not reached should statistical significance.

Discussion

Our study concurred with other studies which showed that finasteride decreases operative blood loss. Hagerty noted decreased episodes of perioperative hematuria in patients pretreated with finasteride. Likewise, the study of John Donohue, et al. determined that finasteride decreased bleeding in TURP patients pretreated with finasteride for 2 weeks.

Puchner and Miller proposed that inhibition by finasteride of conversion of testosterone to dihydrotestosterone leads to a decrease in the androgen derived growth factor responsible for angiogenesis resulting in lesser blood loss. Levels of androgen derived growth factor in the prostate such as fibroblastic growth factor, epidermal growth factor and vascular endothelial growth factor were lower after finasteride administration.

Two weeks pretreatment of inasteride prior to TURP has been shown to decrease blood loss in TURP by Donohue, et al. However, their study added that optimum duration may be shorter or longer depending on the prostate size. In our study, two weeks is a practical period for patients to be pre-treated with finasteride before elective surgery.

The vascular density of BPH has been previously reported. Deering, et al. characterize the vessel density in benign prostatic tissue stained with antibodies to factor VIII-related antigens. Mean vessel density in all transition zones was 70.2. In our study, mean microvessel density showed comparable results. Although the difference was not significant, finasteride administration showed a substantial decrease in mean microvessel density. A longer duration of finasteride administration maybe needed to show a significant decrease and further studies are needed to ascertain the dose and duration of the drug that would provide the expected decrease in microvessel density.

Conclusion

Pretreatment with Finasteride 5mg given daily for 2 weeks in patients with BPH undergoing TURP significantly decreases perioperative bleeding. Finasteride administration also decreases microvessel density in prostatic tissue quantity, however, this has not reached statistical significance.

References


The Safety and Efficacy of Sildenafil Citrate (Viagra™) in the Treatment of Erectile Dysfunction Among Filipino Men: A Real-World Study

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Objective: The aim of the study was to assess the safety/tolerability and the efficacy of sildenafil citrate (Viagra™) in Filipino patients diagnosed with erectile dysfunction (ED) of different etiologies and severity. Methodology: This is an open – label, multi-center study, with the primary objective of obtaining adverse reactions that may occur with the use of sildenafil citrate (Viagra™) 25 mg, 50 mg or 100 mg once daily on as per needed basis, in the out-patient clinic setting across the Philippines. As a secondary endpoint, the study evaluates the efficacy of sildenafil citrate (Viagra™) in the everyday clinical practice of Filipino physicians, using the Patient Global Efficacy Assessment Questions. Safety and toleration were assessed on the follow-up visit using unsolicited and non-leading questioning. All observed and reported events were recorded regardless of a suspected causal relationship to the study drug. Results: Within a three year period, a total 3,955 study participants were enrolled in the study. Majority (57.4%) of the patients were suffering from organic or mixed type (a combination of both psychogenic and organic) of erectile dysfunction while 39.5 percent were of psychogenic origin. Among the adverse events reported by the patients, headache (4.5%), vasodilatation (2.4%) and dizziness (1.7%), showed the highest proportions. Majority (75.1%) reported that these were mild in nature. There were no reported serious adverse events nor were there reported deaths with the use of sildenafil citrate (Viagra™) during the study. Majority (78.9%) reported improvement in their erection after taking the treatment. A fifth (19.8%) of the respondents failed to provide information on this item. However, almost all of the patients were either satisfied or very satisfied with the treatment representing 91.6 percent of the patients. Conclusion: Sildenafil citrate (Viagra™) is a safe and effective medication for the treatment of erectile dysfunction of various etiologies in the Filipino population. Almost all of the patients taking sildenafil citrate (Viagra) were satisfied with the treatment. The results of this study reinforce the proven safety and efficacy profile of sildenafil citrate (Viagra) among Filipino patients with erectile dysfunction.

Key words: erectile dysfunction (ED), sildenafil citrate, safety, tolerability, efficacy
Introduction

Erectile dysfunction (ED) is defined as the persistent inability to achieve and/or maintain an erection sufficient for satisfactory sexual activity and is a common problem in the male population over the age of 40. ED is an important medical condition and overall ED is estimated to affect approximately 100 million men worldwide. In the Massachusetts Male Aging Study, Feldman, et al. found that, in a given population of men between the ages of 40 and 70 years, up to 52 percent will suffer from some degree of ED whether minimal, moderate or complete ED. In Asia, as in other populations, its exact prevalence is unknown. However, if comparable to the United States, the scale of the problem in Asian countries is probably very large.

Numerous physical and psychological factors are involved in normal erectile function, including vasculogenic, neurological, hormonal and cavernosal factors. Abnormalities in one or more of these factors may lead to ED. In most patients with ED, a combination of organic and psychogenic components are involved. According to a review of findings from 6 clinical studies conducted over the past decade, organic factors, with or without psychogenic factors, are present in an average of 78 percent of men with ED. ED is also often associated with co-morbid conditions that may not have been detected previously e.g. cardiovascular disease, diabetes and depression. Additionally, ED-associated distress can have a serious negative impact on the patient’s overall quality of life as well as on interpersonal relationships.

It is therefore important for physicians to be aware of the disease and to diagnose it proactively. The evaluation of a patient with ED should include a determination of potential underlying causes and the identification of appropriate treatment following a complete medical assessment.

Various treatments are available for the management of ED, each associated with a different profile of efficacy, safety, tolerability and patient satisfaction. These would range from radical surgery to parenteral/injectable treatments to oral medications.

Since 1988, when it was first introduced as the first member of a completely new class of drugs, sildenafil citrate (ViagraTM) has gained unprecedented worldwide recognition as oral therapy for erectile dysfunction (ED). Sildenafil citrate (ViagraTM), is the first of a class of drugs that specifically inhibits cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5).

Study Objectives and Design

This is an open – label, multi-center study, with the primary objective of obtaining adverse reactions that may occur with the use of sildenafil citrate (ViagraTM) in the out-patient clinic setting across the Philippines. As a secondary endpoint, the study evaluates the efficacy of sildenafil citrate (ViagraTM) in the everyday clinical practice of Filipino physicians, using the Patient Global Efficacy Assessment Questions. The doses of sildenafil citrate (ViagraTM) used were 25 mg, 50 mg or 100 mg taken once daily on a as needed basis.

Safety and toleration were assessed on the follow-up visit using unsolicited and non-leading questioning. All observed and reported events were recorded regardless of a suspected causal relationship to the study drug.

Results

Within a 3 year period, a total 3,995 study participants were enrolled in the study. The patients’ ages ranged from 20-28 years old with a mean of 54.2 years and median of 55.0 years. More than a third (36.6%) of the patients belonged to 51-60 year age group. (Table 1)

| Table 1. Distribution of patients according to age group. |
|---|---|---|
| No. | %  |
| < 40 | 377 | 9.5 |
| 41 - 50 | 1047 | 26.5 |
| 51 - 60 | 1446 | 36.6 |
| 61 - 70 | 888 | 22.5 |
| < 70 | 165 | 4.2 |
| No information | 32 | 0.8 |
Majority (57.4%) of the patients were suffering from organic or mixed type (a combination of both psychogenic and organic) of erectile dysfunction while 39.5 percent were of psychogenic origin. (Table 2)

Table 2. Distribution of patients according to causality of erectile dysfunction.

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>%</th>
</tr>
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<tbody>
<tr>
<td>Mainly organic or mixed (organic and psychogenic) in origin</td>
<td>2273</td>
<td>57.4</td>
</tr>
<tr>
<td>Mainly psychogenic erectile dysfunction</td>
<td>1561</td>
<td>39.5</td>
</tr>
<tr>
<td>Undetermined</td>
<td>121</td>
<td>3.1</td>
</tr>
</tbody>
</table>

A large proportion (85.9%) of patients claimed to have never used anti-impotence therapy, while 9.9 percent have a history of using treatments for erectile dysfunction. (Table 3). Table 4 shows the anti-impotence drugs (as reported by patients) taken by those who have previously been on anti-impotence therapy. Alprostadil (3.5%), Chinese herbal medicines (2.2%), and Vitamins (1.8%) were the most common anti-impotence treatment utilized by the patients.

Table 3. Distribution of patients as to utilization of anti-impotence therapy.

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ever Used</td>
<td>391</td>
<td>9.9</td>
</tr>
<tr>
<td>Never Used</td>
<td>3396</td>
<td>85.9</td>
</tr>
<tr>
<td>No information</td>
<td>168</td>
<td>4.2</td>
</tr>
</tbody>
</table>

Table 4. Treatment utilized against erectile dysfunction.

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprostadil</td>
<td>140</td>
<td>3.5</td>
</tr>
<tr>
<td>Chinese/herbal medicines</td>
<td>86</td>
<td>2.2</td>
</tr>
<tr>
<td>Vitamins</td>
<td>72</td>
<td>1.8</td>
</tr>
<tr>
<td>Testosterone</td>
<td>32</td>
<td>0.8</td>
</tr>
<tr>
<td>Sulbutiamine</td>
<td>32</td>
<td>0.8</td>
</tr>
<tr>
<td>Sildenafil (Viagra)</td>
<td>15</td>
<td>0.4</td>
</tr>
<tr>
<td>Others</td>
<td>19</td>
<td>0.5</td>
</tr>
<tr>
<td>No information</td>
<td>189</td>
<td>4.8</td>
</tr>
</tbody>
</table>

More than half of the patients diagnosed with erectile dysfunction (52.9%) had concomitant illnesses, the most common of which were diabetes mellitus (25.3%) and hypertension (21.7%). (Table 5)

Table 5. Concomitant illnesses.

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus without mention of complication</td>
<td>1000</td>
<td>25.3</td>
</tr>
<tr>
<td>Unspecified essential hypertension</td>
<td>858</td>
<td>21.7</td>
</tr>
<tr>
<td>Hyperplasia of prostate</td>
<td>119</td>
<td>3.0</td>
</tr>
<tr>
<td>Unspecified hypertensive heart disease</td>
<td>43</td>
<td>1.1</td>
</tr>
<tr>
<td>Asthma, unspecified</td>
<td>42</td>
<td>1.1</td>
</tr>
<tr>
<td>Pure hypercholesterolemia</td>
<td>37</td>
<td>0.9</td>
</tr>
</tbody>
</table>

More than half (52.5%) of the patients included in the study took concomitant medications for other diseases. About 25.7 percent of the patients were taking hypoglycemic agents while 21 percent were on anti-hypertensive agents. (Table 6)

Table 6. Most common concomitant medications taken.

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulphonylurea</td>
<td>704</td>
<td>17.8</td>
</tr>
<tr>
<td>Biguanides</td>
<td>246</td>
<td>6.2</td>
</tr>
<tr>
<td>Undefined insulin</td>
<td>67</td>
<td>1.7</td>
</tr>
<tr>
<td>Calcium-channel blocker, unspecified</td>
<td>449</td>
<td>11.4</td>
</tr>
<tr>
<td>ACE inhibitor, unspecified</td>
<td>162</td>
<td>4.1</td>
</tr>
<tr>
<td>Angiotensin II receptor antagonist, unspecified</td>
<td>80</td>
<td>2.0</td>
</tr>
<tr>
<td>HMG CoA reductase inhibitor, unspecified</td>
<td>72</td>
<td>1.8</td>
</tr>
<tr>
<td>Multivitamin preparation</td>
<td>172</td>
<td>4.3</td>
</tr>
<tr>
<td>Aspirin</td>
<td>65</td>
<td>1.6</td>
</tr>
</tbody>
</table>
**Safety**

Among the adverse events reported by the patients, headache (4.5%), vasodilatation (2.4%) and dizziness (1.7%) showed the highest proportions. Majority (75.1%) reported that these were mild in nature. There were no reported serious adverse events nor were there reported deaths with the use of sildenafil citrate (Viagra™) during the study. A large proportion (98.3%) of patients completed their course of treatment while only 1.7 percent of the patients withdrew from the study. Three patients withdrew due to adverse events while the rest were lost to follow-up.

**Treatment Satisfaction**

The study also assessed treatment efficacy using the Global Assessment Question, the purpose of which is to find out whether the treatment (Sildenafil) improved patients’ erections. Majority (78.9%) reported improvement in their erection after taking the treatment. A fifth (19.8%) of the respondents failed to provide information on this item. However, almost all of the patients treated with sildenafil citrate (Viagra™) were either satisfied or very satisfied with the treatment. This represented 91.6 percent of the patients. The median duration of treatment for the patient population in this study was 12 days. (Table 7)

**Table 7. Distribution of patients according to treatment satisfaction.**

<table>
<thead>
<tr>
<th>Satisfaction</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very satisfied</td>
<td>1793</td>
<td>45.3</td>
</tr>
<tr>
<td>Satisfied</td>
<td>1832</td>
<td>46.3</td>
</tr>
<tr>
<td>Neither satisfied nor dissatisfied</td>
<td>121</td>
<td>3.1</td>
</tr>
<tr>
<td>Dissatisfied</td>
<td>41</td>
<td>1.0</td>
</tr>
<tr>
<td>Very dissatisfied</td>
<td>18</td>
<td>0.5</td>
</tr>
<tr>
<td>No information</td>
<td>150</td>
<td>3.8</td>
</tr>
</tbody>
</table>

**Discussion**

The results of this study gives us a reflection of the real-world usage of sildenafil citrate (Viagra™) in the Philippine setting. Although we lack published data on the prevalence of erectile dysfunction among Filipinos, the study gives us a rough demographic picture of the patients who suffer from the condition. Majority of the patients in this study were in the 40-70 year old bracket, consistent with international epidemiological data which show that erectile dysfunction typically affects men above 40 years old and that the prevalence increases with age. The study also confirms that the typical causes of erectile dysfunction are organic in nature such as chronic illnesses like diabetes and hypertension. Both of these chronic illnesses have vasculogenic and neuropathic affections that explain the increased association with ED.

One of the end-points of the study was to determine efficacy of the treatment. We see from the study that a significant majority of the patients signified that sildenafil citrate (Viagra™) was an effective treatment for erectile dysfunction. This very high treatment satisfaction rate for sildenafil citrate among Filipino patients is not surprising. These data are consistent with already published clinical trial data done among Asians (including Filipinos) and others trials done for sildenafil including another safety monitoring study, the United Kingdom Prescription Event Monitoring Study. The efficacy of sildenafil citrate (Viagra™) has been proven in all types of patients and across all severities. Sildenafil citrate (Viagra™) has an overall average efficacy rate of 80 percent based on previous trials across its dose range. In long term studies done for the product, the favorable treatment satisfaction rating for the sildenafil citrate was sustained over long term even up to 4 years of usage. In a study by McMurray, et al. 96.3 percent of patients on sildenafil citrate (Viagra™) were still satisfied with the treatment even at the 4th year of use. Other possible reasons for this high satisfaction rating are its ideal onset of action and duration of action. One recent study showed that sildenafil citrate (Viagra) had an onset of action that resulted in intercourse as early as 14 minutes in over a third of the patients and almost all patients responded in 20 minutes after the administration of sildenafil citrate (Viagra™). This rapid onset of action can empower the patient with the ability to have an erection when desired.

The main objective of this study was to determine the safety and tolerability of sildenafil citrate (Viagra™) in Filipino patients consulting their physicians in an actual out-patient setting or the real-world setting. Consistent with the pooled analysis of
adverse events in earlier Phase II/III/IV studies, sildenafil treatment was well-tolerated by our patients. Majority of patients did not report any adverse events. For those who experienced adverse events, majority of these adverse events were mild and transient in nature. It is important to note that there were no reported serious adverse events and deaths among the patients taking sildenafil citrate (Viagra™) in this population. A very small percentage of the total study population withdrew from the study and even a smaller percentage discontinued the medications because of adverse events.

A significant number of patients in this study were hypertensive or had concomitant chronic ailments including diabetes. In this population of patients, the effects of any drugs in the cardiovascular system is one of the issues often brought-up. The cardiovascular safety of sildenafil citrate particularly in the population at risk for cardiovascular events, has been the topic of interest of several investigators. Based on these studies, there is now substantial evidence that sildenafil citrate has indeed a favorable cardiovascular safety profile. Sildenafil citrate has no effect on cardiac contractility and heart rate with no clinically significant effect on the QT interval. Its effect on blood pressure is minimal, ranging from 8-10 mmHg systolic and 5-6 mmHg diastolic with no effect on central hemodynamics and with insignificant effect on peripheral vascular resistance. In an elegant study in men with severe coronary artery disease, sildenafil was shown to have no direct adverse cardiovascular effect. Overall, it is important to note that the adverse events reported during this study were expected and consistent with existing published data and with the approved local product labeling.

Conclusions
Sildenafil citrate (Viagra™) is a safe and effective medication for the treatment of erectile dysfunction of various etiologies in the Filipino population. Almost all of the patients taking sildenafil citrate (Viagra™) were satisfied with the treatment. The results of this study further reinforce the proven safety and efficacy profile of sildenafil citrate (Viagra) among ED patients, particularly Filipino ED patients.

References
13. Sildenafil citrate (Viagra™) Local Product Document. As approved by the Bureau of Food and Drugs, Department of Health, Republic of the Philippines.


CASE SERIES

Early Experience in Laparoscopic Renal Surgery for Pediatric Urology: Our Thoughts for the Future*

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Laparoscopic surgery is presently assuming an important role in pediatric urology. It offers minimally invasive surgery to benign real conditions. We report our experience with laparoscopic renal surgery in the pediatric age group and evaluate our series to establish the safety and efficacy of it. Between August 2003 and June 2004, 4 girls with ages ranging from 8 months to 8 years old, averaging 44 months, underwent laparoscopic renal surgeries. Our series consistent of 1 Nephrectomy, 1 Nephroureterectomy (retroperitoneal approach) and 2 Heminephroureterectomies. Operating time ranged from 125 to 340 minutes averaging 185 minutes. Blood loss was minimal. No early or late postoperative complications were noted. Our series also showed that patients experience minimal postoperative discomfort, improved cosmesis and shorter hospital stay with the laparoscopic approach. As we gain more experience refinements in our surgical technique are expected and with the advent of new technology such as Ultrasonic SonoSurg, laparoscopy will be an important facet in the surgical armamentarium of pediatric urologists.

Key words: laparoscopy, renal surgery, pediatric urology

Introduction

Laparoscopic urology is the latest addition to the urologist’s endoscopic skills. Major advances in laparoscopic surgery have enabled less invasive surgery in our urology with the benefits of decreased postoperative discomfort and convalescence as well as improved cosmesis. Initially, laparoscopy was used for the diagnosis and localization of undescended testis but present, it has been extended to therapeutic procedures previously performed solely by open surgical approaches.  

The initial adult laparoscopic nephrectomy and nephroureterectomy were performed in 1990 and 1991 by Clayman and Kerb, et al. respectively. The first pediatric laparoscopic nephrectomy was done in 1992 by Kavoussi and Koyle. In 1992, Figenshau, et al. performed the first pediatric laparoscopic partial nephroureterectomy was described in 1993 by Jordan and Winslow.

We report our experience with 4 laparoscopic renal procedures in children, which to our knowledge are also the first cases to be reported in the country.

Case Series

Between August 2003 and June 2004, laparoscopic renal procedures were performed in 4 girls with a mean age of 44 months. All laparoscopic
operations were performed by the same urologist (DTB). The surgeries performed of 1 nephrectomy, 1 nephroureterectomy and 2 heminephroureterectomies. The transperitoneal approach was performed in 3 patients while 1 patient was operated using the retroperitoneal approach. (Table 2.)

<table>
<thead>
<tr>
<th>General Data</th>
<th>Diagnosis</th>
<th>Procedure</th>
<th>Approach</th>
<th>Operative Time</th>
<th>Hospital Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. C.R.</td>
<td>Left double collecting system with dysplastic upper moiety with ureterocoele and vesicoureteral reflux</td>
<td>Left laparoscopic heminephroureterectomy upper pole Ureterocoelectomy followed by Ureteroneocystostomy with DJ stent placing, lower pole (3/16/04)</td>
<td>Transperitoneal</td>
<td>130 mins</td>
<td>2 days</td>
</tr>
<tr>
<td>2. W.R.</td>
<td>Left dysplastic kidney with ectopic ureter</td>
<td>Left laparoscopic nephrectomy (6/22/04)</td>
<td>Transperitoneal</td>
<td>145 mins</td>
<td>1 day</td>
</tr>
<tr>
<td>3. J.A.</td>
<td>Left dysplastic kidney with ectopic ureteral opening near the bladder neck</td>
<td>Left laparoscopic nephroureterectomy (2/5/04)</td>
<td>Retroperitoneal</td>
<td>125 mins</td>
<td>3 days</td>
</tr>
<tr>
<td>4. S.A.</td>
<td>Right double collecting system with dysplastic upper moiety and ureterocoele</td>
<td>Right laparoscopic heminephroureterectomy (8/28/03)</td>
<td>Transperitoneal</td>
<td>340 mins</td>
<td>8 days</td>
</tr>
</tbody>
</table>

**Case 1. C.R.**

Patient C.R. is a 1 year old female who presented with recurrent febrile UTI, dysuria, and a palpable ballotable hypogastric mass. Ultrasonography showed a double collecting system an upper pole moiety and severe hydronephrosis on the side left. (Figure 1) A DMSA scan showed severely diminished perfusion, tracer uptake and excretion. Cystourethroscopy revealed a huge ureterocoele which was incised draining 100 cc of pus. (Figure 2). On follow-up, voiding cystourethrogram was performed revealing Grade V reflux, left while the voiding phase seemed impeded by the ureterocoele remnant. (Figure 3). Repeat DMSA scan showed decreased cortical tracer activity in the upper half left kidney. (Figure 4)
Case 2. W.R.

W.R. is an 8 year old female who presented with urinary incontinence since birth. Ultrasonography showed a slightly enlarged kidney, right and left kidney. There was no visible ectopic ureteral orifice. IVP showed pyelonephritis, left kidney while CT-scan showed renal hyperplasia in an ectopic left kidney. Retrograde pyelography showed a hypoplastic ectopic kidney left. (Figure 5)

Case 3. J.A.

J.A., a 5 year old female, presented with recurrent febrile UTI. Ultrasonography showed a solitary kidney, right and renal agenesis, left. (Figure 8a, 8b) VCUG was normal. (Figure 10, 11, 12) DMSA scan showed a normal right kidney and a small focus of tracer uptake in left kidney. CT-scan showed a poorly functioning small left kidney. (Figure 9) Retrograde pyelography showed a hypoplastic kidney, right. (Figure 6)
Figure 6. (Patient 3, J.A.) Retrograde pyelography. The hypoplastic right kidney was localized at the level of 4th lumbar vertebrae, corresponding to the level of the iliac crest.

Figure 7. (Patient 3, J.A.) The hypoplastic kidney and proximal ureter (arrow)

Figure 8a. (Patient 3, J.A.) Absent left kidney by ultrasound.

Figure 8b. (Patient 3, J.A.) Normal right kidney.

Figure 9. (Patient 3, J.A.) CT-scan showed poorly functioning small kidney.

Figure 10. (Patient 3, J.A.) VCUG plain film.
and a tortuous and mildly dilated lower pole. (Figures 13a and 13b)

All patients were placed in supine position with a 45º tilt with the affected kidney in the superior portion. A 10 mm trocar was inserted at the umbilicus using an open (Hasson’s technique) which was sutured into the incision. A pneumoperitoneum was created by insufflation of carbon dioxide at 8-10 mm Hg. The telescope was inserted through the umbilical port. Two 5 mm trocars were then placed under direct vision in the subcostal midclavicular and suprapubic midclavicular line (Figures 14 and 15) A third 5 mm trocar was placed in the posterior axillary line in patient 1 and in the costo-vertebral angle in patient 4. The colon was released at the line of toldt, to expose

Case 4. S.A.

S.A. is a 1 year old female presented with recurrent febrile UTI since show was 2 months old. Ultrasonography showed a double collecting system, left with moderate dilatation of the upper pole moiety

Figure 11. (Patient 3, J.A.) VCUG full bladder.

Figure 12. (Patient 3, J.A.) VCUG Post-void showing absence of vesicoureteral reflux (VUR)

Figures 13a and 13b. (Patient 4, S.A.) Double collecting system left with moderate dilatation of upper pole moiety.
the kidney. The ureter was then identified, isolated and dissected in its entire length. (Figure 16)

The vessels of the dysplastic kidney or moiety were then identified, isolated, separated and ligated with automatic clip applicer except for patient 4 (Figure 17) Dissection around the kidneys was continued until it was completely freed.

Figure 16. The uterter was mobilized distally where it was isolated, clipped and divided.

Figure 17. Renal vein was doubly clipped proximally.

The specimens were extracted through the 10 mm umbilical port site without morcellation and enlargement of skin incision. (Figure 7). The trocars were removed individually and the fascial sites were closed with polypropylene (Prolene-0) suture. The skin was closed with polyglactine braided absorbable (Vicryl-4-0) suture.

Results

Average operating time of the laparoscopic procedures including cystoscopy and retrograde pyelography was 185 minutes. There were no intraoperative complications. Postoperative analgesia used during the hospitalization was Paracetamol with a bolus dose of 15 mg/kg and maintenance dose of 500 mL of PNSS + bolus dose x 24 hours.

We analyzed our results by dividing into Group I, heminephroureterectomy (Patients 1 and 4) and Group II, nephrectomy/nephroureterectomy (Patients 2 and 3). (Table 1) In Group I, average operative time was 235 minutes, average blood loss was 40 mL, average post-op hospital stay was 5 days, total number of trocars used was 4, enteral feeding
was resumed with an average of 1-2 days post-op. In Group II, average operative time was 135 minutes, average blood loss was 5 mL, average post-op hospital stay was 2 days, total number of trocars used were 3 and enteral feeding was resumed 0-1 day post-op.

Patient 1 had a better outcome compared to Patient 4 because of the availability of ultrasonic surgery system (SonoSurg) which has improved dissection by doing ligation, cutting and coagulation all at the same time and the decreasing learning curve.

**Discussion**

Laparoscopy is gaining popularity for various procedures in pediatric urology. The primary universal advantages are decreased operative discomfort, decreased hospital stay and improved cosmetic results. Application of laparoscopy to the pediatric population was evaluated by and noted good results. Initial case of pediatric laparoscopic nephrectomy in the local setting showed that it is feasible.

In the series of Ehrlich, et al. and Janetscheck, et al., no intraoperative or post-operative complications were noted similar to ours. Those who underwent heminephroureterectomy for double collecting system had a longer operating time because of greater technical difficulty.

In the aspect of postoperative recovery, early resumption of enteral feeding and short period of hospitalization appeared to be the normal result.

The major disadvantage of laparoscopy is a relatively long operative time due to the steep learning curve. As we gain more experience, however, we believe that operative time will continue to decrease. In addition, the introduction of new technology such as the ultrasonic surgery system (SonoSurg), automatic clip appliers and smaller trocars, we anticipate a further decrease in operative time.

**Conclusion**

Laparoscopy will be an important facet in the surgical armamentarium of pediatric urologists. It is the treatment modality of choice in nephrectomy and heminephroureterectomy for dysplastic kidneys. For heminephroureterectomies however, it is a very viable alternative to open surgery. It is associated with minimal morbidity, minimal post-operative discomfort, improved cosmesis and shorter hospital stay. As we gain more experience and with the advent of newer lap instruments. This, coupled with the purchase of an ultrasonic dissector (SonoSurg), surgery had become obviously easier.

**References**

**CASE REPORT**

**Congenital Adrenal Hyperplasia in Siblings***

Melonil P. Cabahug, MD; Victor Federico B. Acepcion, MD and Marie Carmela M. Lapitan, MD

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Congenital adrenal hyperplasia (CAH) is a family of autosomal recessive disorders of adrenal steroidogenesis with an overall incidence of 1/14,500 live births. It follows a Mendelian form of inheritance with a 25% chance of a child to manifest the symptoms when born from heterozygous parents. Deficiency of 21-hydroxylase is one of the most common causes for ambiguous genitalia. In utero virilization of the fetus consists of clitoral enlargement and vaginal atresia resulting in a urogenital sinus and labioscrotal fusion. We report a case of 3 siblings afflicted with CAH presenting with ambiguous genitalia born from normal, non-consanguineous parents.

**Key words:** congenital adrenal hyperplasia, ambiguous genitalia

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**Introduction**

Congenital adrenal hyperplasia (CAH) is a family of autosomal disorders associated with insufficient cortisol and excess androgenic steroid production. The overall incidence is 1 in 14,500 live births, with certain populations including Ashkenazi Jews and individuals from the Middle East and the Isle de la Reunion having a disproportionately high prevalence. It is also more common in remote regions where consanguinity occurs. In the Philippines, the incidence is 1 per 6025 babies screened. A deficiency of steroid 21-hydroxylase is responsible for 95 percent of cases of CAH; it occurs with an incidence ranging from 1 in 5000 to 1 in 15,000 in the United States and Europe. The highest incidence, 1 in 490, is reported in the Yup’ik Alaskan Eskimo population. Deficiency of 21-hydroxylase is one of the most common causes for ambiguous genitalia or pseudohermaphroditism. Males and females are affected with equal frequency, and the affected individuals are almost always born in only one generation of a family. The child of 2 heterozygous parents has a 25 percent chance of being homozygous.

The incidence of CAH among siblings has rarely been reported. We report the cases of 3 siblings with CAH presenting with ambiguous genitalia.

**Case Reports**

Sister 2, sister 3 and sister 4 were noted to have ambiguous genitalia at birth. Their parents are non-consanguineous, and have no family history of ambiguous genitalia. Sister 1 and sister 5 are normal. All 3 affected siblings are reared as girls.

Sister 2 was noted to have clitoral enlargement at birth, with episodes of on and off vomiting associated with fever and chills. She eventually

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* Second Place Winner, 10th St. Luke’s Urology Case Presentation Contest.
expired at 3 months of age with no work-up done. The actual diagnosis was unknown to the family. Sister 3 and sister 4 were also noted to have clitoral enlargement at birth. They were brought for medical attention at ages 3 years old and 3 months old, respectively, when they began to have on and off vomiting. Physical examination showed enlarged clitoris and fused labial folds with a single opening for the vagina and the urethra. (Figures 1, 2, 3 and 4). There was note of other virilizing signs like hirsutism and pubic hair in sister 3.

Laboratory workup for both sister 3 and sister 4 revealed elevated 17-OH progesterone (17-OHP), hyponatremia, and hyperkalemia. Karyotyping done showed 46, XX karyotype for both children. Abdominal ultrasound done showed normal internal reproductive organs and adrenals. A diagnosis of CAH was made and both patients were given prednisone and NaCl supplementation. Sister 3 initially underwent a diagnostic laparoscopy, which showed the presence of a normal uterus, fallopian tubes and ovaries and a normal vaginal wall. Genitoscopy confirmed the suspicion of a urogenital
sinus. She then underwent a feminizing genitoplasty, which included clitoroplasty and labioplasty. The long term plan is to perform vaginoplasty when patient reaches 12 years old. Follow-up at 4 weeks post-operatively showed the previously large clitoris to have decreased to an acceptable size with more aesthetic looking labial folds. (Figure 5). Sister 4 is still being prepared for feminizing genitoplasty and vaginoplasty.

Discussion

CAH is a family of autosomal recessive disorders of adrenal steroidogenesis. It usually follows up Mendelian pattern of inheritance such that the children of the affected (homozygous) person are all heterozygotes and the children of a homozygote can only be affected if the spouse is a heterozygote. Thus, there is only a 25 percent chance of a child with heterozygote parents to have CAH. Unfortunately, in our case, no genetic studies were done on the parents, due to financial constraints.

The gene is HLA-linked on the short arm of chromosome 6. The most commonly recognized syndromes result from a deficiency of one of the terminal two enzymes of glucocorticoid synthesis (21-hydroxylase or 11-hydroxylase) resulting to impaired hydrocortisone formation, causing compensatory increase in the secretion of adrenocorticotropic hormone (ACTH). The deficiency in cortisol results in increased secretion of corticotrophin, which in turn, leads to adrenocortical hyperplasia and overproduction of intermediary metabolites. Our patients had normal-sized adrenal glands on abdominal ultrasound.

The most common of the genetic defects of steroidogenesis (<90% of cases), is CYP21 defects. Two CYP21 genes are located on chromosome 6 (6p21.3). The CYP21 gene encodes the enzyme P450c21 that converts 17-OHP to 11-deoxycorticosterone and 11-DOC, respectively. The pseudogene is called CYP21P. The high similarity between both genes allows genetic recombination and is one of the causes for the high incidence of abnormalities involving CYP21. There is a high correlation between genotype and phenotype, allowing DNA analysis to predict, with certain reliability, the enzyme activity and consequently, clinical presentation. Most patients are compound heterozygotes and consequently, the degree of loss of enzyme activity and therefore the phenotype, will depend on the relative severity of the mutations in each of the 2 alleles of the gene. The mutant allele associated with the less severe loss of enzyme activity will determine the phenotype. HLA-BW47 is associated with salt-wasting forms while HLA DR1, B14 are associated with non-classical forms of CYP21 defects.

Clinically, patients are divided into three categories: salt wasters (patients with virilization and aldosterone deficiency); simple virilizers (patients with virilization, but without salt wasting); and nonclassic patients (those without evidence of virilization or salt wasting). In patients with the salt-losing variant, patients cannot adequately synthesize aldosterone due to the severely impaired 21-hydroxylation of progesterone. Deficiency of this hormone leads to sodium loss via the kidney, colon and sweat glands. Severely affected patients invariably have concomitant cortisol deficiency, which exacerbates the effects of aldosterone deficiency. In the absence of glucocorticoids, cardiac output decreases. This decreases glomerular filtration, leading to an inability to excrete free water and consequently to hyponatremia. Thus, shock and severe hyponatremia are much more likely in 21-hydroxylase deficiency, in which both cortisol and aldosterone biosynthesis are affected. Salt wasting may include non-specific symptoms such as poor appetite, vomiting, lethargy and failure to gain weight. Severely affected patients with CAH usually present at 1-4 weeks of age with hyponatremia, hyperkalemia, hyperreninemia and hypovolemic shock. These adrenal crisis may be fatal.
if proper medical care is not delivered. A closer review of sister 2’s clinical course and death circumstances demonstrates that she may have been a salt-waster who did not receive the appropriate treatment. Fortunately, the diagnosis was clinched for the younger sister 3 and 4 and the management instituted before serious complications developed.

Newborn females with the classic presentation of 21-hydroxylase deficiency may have urogenital sinus, scrotalization of the labia majora, labial fusion, clitoromegaly or formation of penile urethra. Bone age is usually advanced and these children are at risk for short stature in adulthood. Although only clitoromegaly was documented in sister 2, clitoromegaly, urogenital sinus, scrotalization of the labia majora, and labial fusion, were all documented in Sister 3 and Sister 4. Their height is still at par with age.

Diagnosis of CAH should always be suspected in the following situations: any child with ambiguous genitalia including isolated bilateral cryptorchidism; newborns presenting with shock and dehydration; males or females with signs of inappropriate virilization; children with hypertension and hypokalemia; females with lack of secondary sex characteristics.

Diagnosis rests on measurement of markedly elevated levels of 17-OHP in the serum. CAH in an infant or child should always alert one to the diagnosis in later siblings. HLA family studies have shown that affected siblings share the same HLA type. Thus, after the birth of an affected infant, HLA typing of amniotic fluid cells, as well as measurement of elevated 17-OHP in amniotic fluid, may permit prenatal diagnosis is subsequent pregnancies. In our case, had the diagnosis of CAH been established with sister 2, amniotic fluid studies would have allowed early identification of the problem in sister 3 and sister 4. Closer monitoring and anticipatory management may have been done to prevent the occurrence of masculinization and the development of symptoms of salt-wasting.

After birth, masculinization progresses. Pubic and axillary hair develops prematurely, acne appears and voice assumes a masculine quality. Ossification is advanced. Unfortunately, no bone studies have been done on sister 3 and sister 4 due to financial constraints. Voice change and height discrepancy were not seen in both patients, but other secondary sexual characteristics like pubic hair was seen in sister 3. Most patients with 46, XX karyotype are raised as girls.

The mainstay in the treatment of CAH is glucocorticoid. The goal is to reduce serum concentrations of ACTH and consequently the drive for the synthesis of androgens. The near-normalization of the androgen levels should prevent further inappropriate virilization and advancement of bone age. Patients with the salt-losing variant may require a mineralocorticoid and sodium supplementation in addition to the glucocorticoid. Both patients are maintained on Prednisone at 10 mg/m2/day and NaCl supplementation.

The enlarged clitoris of female infants usually requires surgical correction. Whether, how and when to intervene surgically in the correction of genital anomalies is the subject of continuing debate. Some adult patients with CAH and other intersex conditions who are unhappy with their gender assignment, as well as some physicians, have advocated postponing genital surgery until the affected individual is able to provide informed consent for cosmetic genital surgery and select the gender with which he/she will be most comfortable. Most investigators, however, suggest earlier timing of surgery. Reasons for this early intervention include better compliance with dilatation, lessening of the parents’ concerns regarding their “anomalous child” and the assumptions that the child later in life does not remember early interventions. One follow-up study by Randolph, et al. reported outcomes as “excellent” in 27 out of 37 patients undergoing clitoroplasty in the newborn period. Another study by Lobe, et al. looked at 58 patients undergoing surgery at a variety of ages and found that there were more complications in the group diagnosed and operated on later in life as compared with the group diagnosed and operated on as infants. Surgical reconstruction consists of early clitoroplasty, vaginal pull-through and labioplasty. Recession of the clitoris should be performed, rather than its removal. Vaginoplasty and correction of the urogenital sinus is usually performed at the time of clitoral surgery.

Later revisions may be necessary. Sister 3 underwent clitoroplasty where the clitoris was degloved and the erectile tissues removed. At the same time labioplasty was done where the preputial skin was divided and used to create a labia minora and the Y-V plasty done to create the labia majora. Sister 4 is still for surgical reconstruction.

In summary, we presented the case of 3 siblings affected with congenital adrenal hyperplasia who manifested with ambiguous genitalia and salt-wasting. The genetic basis for the disease as well as
the clinical presentation was discussed. Medical and surgical management issues were also tackled.

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CASE REPORT

Nerve Sparing Radical Prostatectomy in an 18-year-old Boy with Localized Poorly Differentiated Adenocarcinoma*

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Department of Urology, East Avenue Medical Center

Prostate cancer is predominantly a disease of the elderly male, with more than 75 percent diagnosed older than 65 years. Occurrence of the disease is uncommon in those less than 50 years of age and very rare in the adolescent. The case presented is an 18 year old male who went into urinary retention with associated significant weight loss and gross hematuria. Patient was diagnosed to have clinically localized prostate adenocarcinoma. He underwent radical prostatectomy. Based on literature search, this is the youngest reported case of prostatic adenocarcinoma in the Philippines, the 3rd youngest case in the world and the youngest case of localized prostate cancer who underwent radical prostatectomy.

Key words: prostate, adenocarcinoma, localized prostate cancer, adolescent, radical prostatectomy

* Third Place Winner, 10th St. Luke’s Urology Case Presentation Contest.

Introduction

Adenocarcinoma of the prostate is the 4th most common male malignancy worldwide. It is predominantly a disease of the elderly male with 75 percent of new cases diagnosed among men 65 years old and above (Figure 1). The current trend however shows that it is becoming a disease of the middle age men whose ages ranged from 50-59. It is uncommon among young adults less than 50 years old and very rare in the adolescent age group (< 21 years old). Review of literature shows only five cases of prostate adenocarcinoma in the adolescent. All of these cases presented with an advanced disease and most eventually died after hormonal therapy. None were good candidates for radical prostatectomy.

Case Report

This is a case of an 18-year old male who had a two month history of moderate to severe lower urinary tract symptoms with an associated significant weight loss (approximately 30%) and constipation. He sought consult and was diagnosed with acute bacterial prostatitis and managed with oral antibiotics. Symptoms however persisted with note of gross hematuria and subsequent urinary retention. Patient was then brought to the hospital where a foley catheter (Fr 16) was inserted with slight difficulty and with one liter of tea colored urine evacuated. On physical examination, he was conscious, coherent, and pale-looking, but with stable vital signs. Digital rectal examination revealed a grade III enlargement of the prostate gland which was smooth, firm, non-movable and slightly tender. Other organ systems were normal. Both medical and family histories were non-contributory.

A KUB and prostate ultrasound done revealed a solid nodular mass approximately 90 grams, located
posterior to the urinary bladder. Both kidneys and urinary bladder were normal. Intravenous urography showed normal upper urinary tracts with an extrinsic compression noted at the base of the bladder (Figure 2). Prostate specific antigen (PSA) result was within normal levels at 2.59 ng/dl.

The patient underwent cysto-urethroscopy which revealed a markedly enlarged prostate almost completely obstructing the urethra. The bladder was noted to be normal. A digitally guided transrectal biopsy of the prostate was then done.

Microscopic examination of tissues obtained disclosed tumor cells arranged in cords and in solid masses infiltrating the fibromuscular stroma and destroying the normal glandular pattern favoring adenocarcinoma.

Liver function test and serum alkaline phosphatase were normal. Chest x-ray was also normal. Abdominal CT scan revealed a well encapsulated markedly enlarged prostate with no evidence of lymph node metastasis (Figure 3). The liver as well as the gastrointestinal tract was noted to be normal and no other abdominal mass was noted. Flexible colonoscopy was normal. Bone scan did not show bone metastasis (Figure 4).
Patient was clinically staged as T2bN0M0 (Table 1). After informed consent, the patient underwent a nerve sparing radical prostatectomy with bilateral pelvic lymphadenectomy (Figures 5 and 6). There was no gross involvement of the pelvic lymph nodes.

Table 1. Prostate cancer staging system.

<table>
<thead>
<tr>
<th>TNM</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tx</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>To</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumor found in tissue removed at TUR: 5% or less is cancerous with histologic grade &lt; 7</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumor found in tissue removed at TUR: &gt; 5% is cancerous or histological grade &gt; 7</td>
</tr>
<tr>
<td>T1c</td>
<td>Tumor identified by prostate needle biopsy owing to elevated PSA</td>
</tr>
<tr>
<td>T2a</td>
<td>Tumor involves one lobe or less</td>
</tr>
<tr>
<td><strong>T2b</strong></td>
<td><strong>Tumor involves more than one lobe</strong></td>
</tr>
<tr>
<td>T3a</td>
<td>Unilateral extracapsular extension</td>
</tr>
<tr>
<td>T3b</td>
<td>Bilateral extracapsular extension</td>
</tr>
<tr>
<td>T3c</td>
<td>Tumor invades seminal vesicles</td>
</tr>
<tr>
<td>T4a</td>
<td>Tumor invades bladder neck, external sphincter, and/or rectum</td>
</tr>
<tr>
<td>T4b</td>
<td>Tumor invades levator muscle and/or fixed to pelvic wall</td>
</tr>
<tr>
<td>Nx</td>
<td>Regional lymph nodes can not be assessed</td>
</tr>
<tr>
<td><strong>N0</strong></td>
<td><strong>No lymph node metastasis</strong></td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in single regional lymph node &lt; 2 cm in dimension</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis in single (&gt; 2 but &lt; 5 cm) or multiple nodes with none &gt; 5 cm</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in regional lymph nodes &gt; 5 cm in dimension</td>
</tr>
<tr>
<td>Mx</td>
<td>Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>No evidence of distant metastasis</td>
</tr>
<tr>
<td>M1a</td>
<td>Involvement of non regional lymph nodes</td>
</tr>
<tr>
<td>M1b</td>
<td>Involvement of bones</td>
</tr>
<tr>
<td>M1c</td>
<td>Involvement of other distant sites</td>
</tr>
</tbody>
</table>
Figure 5. Nerve sparing radical prostatectomy.

Figure 6. The excised prostate gland.

Figure 7. Histopathology slides showing sections of tumor cells arranged in cords and in solid masses infiltrating the fibromuscular stroma, destroying the normal glandular pattern.

Figure 8. Sections of pelvic lymph nodes shows no evidence of metastasis.

Final histopathology report was Adenocarcinoma of the prostate gland, with a Gleason’s score of 10 (5 + 5). (Figure 7) Section of both right and left lymph nodes did not show any evidence of metastasis. (Figure 8) Final pathologic stage is IIB (T2N0M0) (Table 1).

Postoperative course was uneventful. Postoperative morning erections were noted. He was then discharged on the 12th post-op day. Foley catheter was removed on the 21st postoperative day.

Discussion

Presented to us is an 18 year old boy with an enlarged prostate gland who went into urinary retention, associated with gross hematuria, a significant weight loss of 30 percent in 3 weeks and anemia. Rhabdomyosarcoma was initially considered because of the findings on digital rectal examination and the normal PSA value. Malignancy of a non-prostatic origin was also considered. Abdominal CT scan and colonoscopy did not reveal any other primary tumor. Final histopathology after radical prostatectomy was prostatic adenocarcinoma with a Gleason score of 10 confirming that the tumor is to be primarily prostatic in origin.

As familial genetic predisposition is common in prostate adenocarcinoma in the young, the patient’s father, a 43-year old man, underwent screening for prostate cancer. A mildly enlarged, smooth, firm, movable prostate with a hard right lobe
was noted on digital rectal examination. Serum PSA was within normal levels at 0.63ng/dL. A transrectal ultrasound-guided biopsy of the prostate was done revealing a benign prostate on histopathology. No history of any other cancer was noted in the family.

The patient had been exposed for about five years to the chroming business and worked for two months in the textile industry. These have not been identified as potential risks to the development of prostate cancer.23, 24 Based on an extensive review of existing journals and MEDLINE search by MeSH database, this is the youngest documented case of prostate adenocarcinoma in the Philippines and the 3rd youngest case of prostate adenocarcinoma in the world. This is also the youngest male in the world with a clinically localized prostate carcinoma who underwent radical prostatectomy.

Five cases of prostate cancer in the adolescent male have been reported. The youngest was an 11-year-old had undifferentiated prostate cancer noted on autopsy.12 The youngest case diagnosed antemortem was of a 15 year-old male13 the next youngest was that of a 17 year old male14 next youngest case was of a 19 year old male15 and the last case was that of a 20 year old male.16 All cases presented with a poorly differentiated to undifferentiated prostate adenocarcinoma that were locally advanced to metastatic at presentation no longer amenable to surgery. Only the 20 year old with poorly differentiated and locally advanced prostate cancer survived more than 5 years with complete androgen blockade.

The case presently being presented is of a poorly differentiated adenocarcinoma (Gleason 10), which was clinically localized (T2bNoMo) at initial diagnosis and underwent nerve sparing retropubic radical prostatectomy.

Appropriate treatment for prostate carcinoma in the young is still debatable as only few cases are encountered. These are aggressive tumors that are local or far advanced on presentation. The question is on whether these tumors behave like those in the elderly male, stage for stage. Studies have shown that radical prostatectomy for a clinically localized prostate cancer in men younger than 50 years of age has been shown to have a greater long term cancer control rates than the elderly male.5, 25, 26 It remains to be seen whether this is also true with the adolescent male. With limited cases at hand, the surgeon is inclined to institute management according to stage based on studies of prostate cancer in older males.

Based on several studies, radical prostatectomy as primary treatment for a clinically staged T2bN0M0 prostate cancer has a progression free rate by PSA of 77-80 percent in 5 years. Based on the gleason score of 10, the 5 year non progression rate is between 41-74 percent. With the PSA value of 2.59 ng/dl, the 5-year non-progression rate is between 94-95 percent. It the pathologic stage is T2bN0M0 the progression free rate is 91-95 percent.27-31 Therefore the clinical and pathologic stage as well as the preoperative PSA shows a good prognosis for the patient with radical prostatectomy alone. The gleason score however shows poor prognosis with a greater chance of progression with radical prostatectomy alone.

More convincing evidence that radical prostatectomy can sufficiently control the disease is the long term result of surgery for 174 cases with gleason scores of 7-10 on needle biopsy.32 In the reanalysis of the study, 32 percent were pathologically organ-confined; only one patient progressed after follow-up.33 In another study involving 1,199 patients with Gleason scores of 8 or higher, 57 percent were pathologically confined. The 5 year disease free survival rate was 84 percent.34

Radical prostatectomy alone would therefore seem to be the logical approach in this case with close follow-up and monitoring. However, with the initial PSA within normal limits and the poorly understood behavior of prostate cancer in the young, the question arises on whether PSA monitoring would be the reliable tool in determining tumor progression. The logical approach would be to institute adjunctive hormonal radiotherapy in the setting of PSA progression which is defined as a level of > 2 0.2 ng/ml and rising on at least two subsequent occasions after radical prostatectomy.35 But if the PSA should fall below this level, is it safe to assume that there is no tumor recurrence? Recurrence after radical prostatectomy has been documented in the absence of undetectable PSA levels.36-39 This datum, added to the poorly understood behavior of prostate carcinoma in the young favors periodic work-up with chest radiographs, liver assays, alkaline phosphatase, abdominal CT scan and bone scan.

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Metastatic Renal Cell Carcinoma in the Contralateral Adrenal Gland of a 65 year old Male 10 Years After Radical Nephrectomy

Lou Chris Allen H. Reyes, MD; Demetrio R. Hadap, MD and Josefino C. Castillo, MD

A case of a 65 year old male from Tondo, Manila with metastatic Renal Cell Carcinoma (RCC) in the contralateral adrenal gland is presented. He underwent a left radical nephrectomy back in May 1992 after which he remained asymptomatic. Only the finding of a right adrenal mass 10 years later would stand to challenge his “cured” state. The steps that lead to the diagnosis and the subsequent management of his case are discussed here.

Key words: renal cell carcinoma (RCC), metastasis, adrenal mass

Introduction

Renal cell carcinoma (RCC) is known to be the most lethal of the urologic cancers. Approximately 50 percent of all patients diagnosed with it either present with metastases at diagnosis or will have metastatic disease after nephrectomy.1 It accounts for about 2 percent of all malignancies, with a worldwide increase of 1.5 – 5.9 percent per year. The mean age at the time of diagnosis is about 70 years and there is a predominance of men over women in the range of 1.5 – 3.1.2,3 With such a propensity to metastasize, the organs it involves are varied. In the order of decreasing frequency, these are as follows: lung (50% to 60%), bone (30%), lymph nodes (30%), liver (30%), brain, contralateral kidney, pancreas, skin (5% to 15%) and ipsilateral adrenal gland (5 to 10%). Against the low incidence of an ipsilateral metastasis, that of a solitary metachronous involvement of the contralateral adrenal gland is even rarely diagnosed and only a few have been reported.4,5,6 Presented here is a case of a 65 year old male with a right adrenal mass discovered 10 years after a left radical nephrectomy. An adrenalectomy was subsequently performed, from which a diagnosis of metastatic renal cell carcinoma was obtained.

Case Report

This is a case of 65 year old male from Tondo, Manila who was discovered to have a left renal mass back in May 1992 at another institution. There, he underwent a left radical nephrectomy with regional lymph node dissection (Figure 1). The surgical pathology report gave a diagnosis of Renal Cell Carcinoma, tubulo-papillary, Stage II. All the lymph nodes turned out negative for tumor cells, as did the left adrenal gland. The patient was subsequently discharged improved but was lost to follow up with that institution.

The patient later sought consult at our institution in March 2002 when he began to note occasional right flank pain beginning the month earlier. An ultrasound was requested and an incidental adrenal mass on the right was noted. This was followed-up with an MRI of the abdomen which confirmed the right adrenal mass measuring 5.7 x 4.8 x 4.9 cm (Figure 2). A percutaneous adrenal mass biopsy...
under CT guidance was recommended and he was referred to Endocrine service for work-up. Serum aldosterone, plasma renin, urine metanephrine, and serum cortisol levels were checked and were all noted to be within normal limits, ruling out a functioning adenoma. Due to financial constraints, however, he was only able to have the percutaneous biopsy done five months later, August 2002. The histopathology from the CT guided aspiration reported bloody smears, precluding a definitive diagnosis. He was advised close follow-ups and requested to have CT scans of the abdomen every 6 months. His next CT scan in March 2003 showed the adrenal mass to measure 6.0 x 5.0 cm. while that done in September 2003 showed the adrenal mass to have increased in size to 7.0 x 5.2 cm. On his next follow-up in October 2003, he was advised to undergo adrenalectomy. The patient was then referred to the Endocrine and Medicine service for pre-operative clearance. Early the following month, November 2003, patient was cleared for surgery.

On admission, the patient was started on Solucortef 100 mg IV given every 6 hours. He was asymptomatic with stable vital signs, remaining normotensive throughout his hospital confinement. Physical examination revealed essentially normal findings save for a 20 cm left paramedian incision scar in the abdomen. The patient subsequently underwent right adrenalectomy, by the thoraco-abdominal approach under general endotracheal anesthesia (Figure 3). On dissection, the adrenal tumor was noted to be well-encapsulated, allowing en-bloc excision of the mass (Figure 4A). On cut-section, it appeared to be multi-cystic (Figure 4B). The specimen was sent for histopathologic studies. About 2 to 5 grams of normal appearing adrenal gland was left. Intraoperatively, as with the postoperative course, the patient remained stable. A thoracostomy tube was left in place, which was removed by the 2nd postoperative day. Also, the Solucortef dosage was decreased to 100 mg IV given every 8 hours. By the 4th postoperative day, the penrose drain was removed and the patient’s Solucortef dosage was decreased further to 50 mg IV given every 12 hours. By the 5th postoperative day, the patient was discharged home with a tapering dosage regimen of oral Prednisone 5 mg/tab over the next weeks.
Histological examination of the specimen demonstrated metastatic renal cell carcinoma in the right adrenal gland. The patient was then advised to have another CT scan of the abdomen after 3 months (February 2004). However, the patient again was unable to comply but was finally able to have the diagnostic procedure done last July 2004. A nodular density measuring 2.5 x 1.6 cm was seen superior to the right kidney. Post-surgical changes, were considered; tumor recurrence ruled out. The patient had no subjective complaints. However, his blood pressure was noted to be more elevated, ranging from 130-150/80-90. His creatinine value was stable at 2.1 mg/dL. The patient was then maintained on Prednisone 5 mg/tab once daily and Metoprolol 50 mg/tab ½ tab daily.

Discussion

Renal Cell Carcinoma (RCC) remains to be the most challenging urologic malignancy. With its cure depending strongly on the stage and grade of the disease, the time of diagnosis is crucial to survival. In so much, however, that the cancer is localized on diagnosis, the mainstay of treatment is radical nephrectomy. The classic description of radical nephrectomy includes excision of the kidney with all of the Gerota’s fascia and removal of the ipsilateral adrenal gland; regional lymphadenectomy may also be included in the surgery.

The recommended postoperative surveillance for localized RCC – with a pathologic tumor stage of T2N0M0 – after radical nephrectomy is a chest x-ray every year and an abdominal CT scan every 2 years. A diligent follow-up is needed from these RCC patients. The goal of which is to detect local recurrences and distant metastases as early as possible to enable additional treatment when indicated.

Metastasis to the adrenal glands from RCC has been reported in 1.6 – 3.6% of patients. The incidence of the localization in the adrenals is probably explained by the type of adrenal blood supply, by their high flow volume and by the type of their capillary network, which has a sinusoidal vascular pattern. RCCs, which are vascular tumors, will most definitely favor this system.

In the nephrectomized patient, the incidence of contralateral adrenal gland metastasis is only 0.7 percent. Two articles from opposite sides of the world report cases of contralateral adrenal gland metastasis from RCC. The first, from Japan, notes a synchronous occurrence while that from France describes a metachronous manifestation. A group from the Mayo Clinic reviewed their experience with contralateral adrenal metastasis from October 1978 to April 2001 and came up with 11 patients, two with synchronous metastases and nine with metachronous metastases.

Clinical signs and symptoms of metastatic RCC to the adrenal gland are rare and adrenal insufficiency is not a common finding. The silent nature of such metastases is explained as is known that even one tenth of the remaining adrenal tissue is capable of regulating all normal body functions without the appearance of adrenal insufficiency and with normal cortisol and adrenaline values in the blood. Because of this asymptomatic feature of metastatic RCC, vigilant surveillance becomes paramount. Low-grade, low-stage renal cell carcinoma carries a good prognosis. It is therefore desirable to diagnose metastatic lesions while they are solitary and small.

It is quite fortunate that the patient developed right flank pain for which an imaging study was requested. The chief method of detection of adrenal metastasis is by CT scan, wherein the appearance of these adrenal masses have characteristics similar to those of solid renal tumors. MRI gives just as good information but has its advantage against a non-contrast CT scan.

Early diagnosis of RCC metastasis facilitates immediate treatment. Since there is still no effective
adjuvant treatment for metastatic renal cell carcinoma, aggressive surgical therapy is advocated for solitary deposits of this disease. In cases of apparently solitary metastatic RCC lesions, as reported at the University of Texas MD Anderson Cancer Center, resection of these tumors carry an overall 5-year survival rate of 29-35 percent. In another report, 5-year survival rates between 63 percent and 75 percent were reported in select patients following the resection of solitary glandular or soft tissue metastases and a solitary site of recurrence is associated with an improved prognosis. Patients who developed a metachronous solitary metastasis fared better than those with a synchronous solitary metastasis (5-year survival rates of 39% and 22%, respectively), regardless of the site.

In cases of solitary metastatic RCC lesions to the adrenal glands, it is best managed with adrenalectomy. Removal of solitary metastases from renal cell carcinoma has been reported with therapeutic success and prolonged survival. This was also attested to by the Mayo Clinic review, which concluded that surgical resection of contralateral adrenal metastasis from RCC is safe; although most patients died from RCC, survival may be prolonged in individual patients.

These patients, who underwent radical nephrectomy and are now having adrenalectomy may be rendered adrenally insufficient and so they may require lifetime replacement therapy with corticosteroids. Close monitoring of such patients is mandatory to adjust properly the amount of steroid replacement and to avoid complications of adrenal insufficiency or excess.

In addition, metastatic RCC in the adrenal must be differentiated from adrenal cortical carcinoma. Foucer and Dehner reported on 2 patients in whom contralateral adrenal metastases from renal cell carcinoma were misdiagnosed as adrenal cortical carcinomas. Immunohistochemical staining for epithelial membrane antigen has been reported to be positive in RCC and negative in adrenal tumors. The histopathology report of the adrenal mass stated that the tumor cells were reactive to both vimentin and cytokeratin. Adrenal cortical tissue will react with vimentin, identical to RCC cells but it is not known to be reactive to keratin, thereby differentiating the two.

Contralateral adrenal gland metastasis after radical nephrectomy for renal cell carcinoma rarely occurs. Patients are generally asymptomatic and will usually show no signs of adrenal insufficiency. This makes follow-up surveillance crucial in the further management of post radical nephrectomy patients. The recommended bi-annual CT scan of the abdomen proves to be effective in monitoring for such metastasis as the median time to relapse in this particular pathologic stage was noted to be about 25 months. The earlier solitary sites of recurrence are detected, the faster aggressive surgical resection can be carried out, giving an improved prognosis. The patient, having undergone surgery, should also be regularly seen by the Endocrinologist. In the end, a close follow-up of these post radical nephrectomy patients will spell the difference between borrowed time and an extended life.

References


Orbital Tumor from Renal Cell Carcinoma

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Orbital tumors are rare. Age specific incidence of primary malignant orbital tumor is approximately 2 per 1 million population until the 6th decade, 4 per 1 million in those older than 60 and 10 per 1 million in those older than 80 years.1 Approximately 1-13 percent of all orbital tumors are metastatic in nature.2 The most common primary cancers that metastasize to the orbits are breast, prostate gland and lung. In a series of 100 patients with orbital metastasis, only 5 patients had primary cancer from the kidney.2 We report a case of an orbital tumor which turned out to be a metastasis due to a renal cell carcinoma from the contralateral kidney.

Key words: renal cell carcinoma, orbit, metastasis

Case Report

A 20-year old male with no known medical illnesses or previous surgeries had a 2-month history of a non-tender left upper lid swelling. This was associated with foreign body sensation in the eye, occasional tearing and blurring of vision. Self medication with tetrahydrozaline was done with eventual resolution of symptoms but with residual ptosis. One month hence, there was note of gradual proptosis, conjunctival suffusion, foreign body sensation in the eye and tearing not relieved with intake of oral antibiotics. Ocular examination done showed uncorrected visual acuity of 6/6, right eye, 6/21, left eye. Grossly, there is marked periorbital swelling of the left eye with downward and medial proptosis of the left globe (Figure 1). The conjunctiva was chemotic with exposure keratitis of the lower quadrants. Pupils were briskly reactive to light, but ductions of the left eye were limited on all aspects. Intraocular pressure was slightly increased on the left eye.

Initial physical examination, chest x-ray, ECG, urinalysis and hematologic studies revealed normal findings. Orbital CT scan done showed a 3.6 x 2.8 x 3.5 cm heterogeneously enhancing extraconal mass in the left orbit anterosuperolateral in location, with intracranial extension (Figure 2). There was associated erosion of the left orbital floor, frontal process of the zygoma, frontal bone and greater wing of the sphenoid bone. This initial impression was a lacrimal gland tumor on the left, with consideration for an adenoid cystic carcinoma.

Excision biopsy of the left orbital mass was done. Histopathologic examination showed several nests and cords of polyhedral cells with pleomorphic nuclei and abundant clear to granular cytoplasm with several areas of necrosis and bone destruction, consistent with an adenocarcinoma with clear cell
features, probably metastatic. Immunohistochemical studies done (cytokeratin and vimentin) showed positive results suggestive of metastatic renal cell carcinoma, clear cell type.

Figure 1. Periorbital swelling of left eye with proptosis.

Figure 2. Orbital CT scan showing left orbital mass with intracranial extension.

Abdominal ultrasonography done showed an enlarged right kidney with a well circumscribed heterogeneous solid mass (8.7 x 9.0 x 7.7 cm) in the mid portion. The inferior calyces were intact but the rest of the central echo complexes were not demonstrated. The left kidney, urinary bladder, liver
and gallbladder were normal. On abdominal examination, there was note of a 6 x 8 cm fixed, nontender mass at the right hemiabdomen. An abdominopelvic CT-scan revealed a huge heterogenous mass with calcifications arising from the superior pole of the right kidney, involving the middle end portion of the inferior pole. It measured 14 cm in the craniocaudad dimension and 8 cm in width (Figure 3).

![Figure 3. Abdominopelvic CT-scan showing renal mass, right.](image)

The patient was advised regarding the general prognosis of his illness and nephrectomy with adjuvant chemotherapy and immunotherapy was recommended. The patient, however, refused to undergo further treatment.

**Discussion**

The orbit is an unusual site for metastatic cancer.² It represents only 5 percent of the orbital tumors in children and 8 percent in the older population. Renal cell carcinoma metastatic to the orbit has been reported. When this tumor spreads to the orbit, the orbital metastasis is likely to be the first indication of the cancer. No local incidence of renal carcinoma metastatic to the orbit is available at present, but it was documented to be 4.9 percent in Japan and 0-7 percent in the US.³

The first reported pulsatile metastatic orbital tumor from renal cell carcinoma was reported by Howard, et al. in 1978(4). Ocular manifestations include proptosis associated with a large, pulsatile, collapsible mass simulating a vascular neoplasm. This was further associated with an extensive bone destruction demonstrated on CT and routine radiographic study, rarely seen in primary orbital tumors. It was suggested that pulsatile exophthalmos acquired in the middle age associated with significant bone destruction represents a constellation of findings most consistent with a metastatic tumor probably renal carcinoma. These findings appear to be similar with that in our present case.

Systemic metastases portend a particularly poor prognosis for renal cell carcinoma and orbital metastasis is no exception. Among patients with renal cell carcinoma with orbital metastases, the time from appearance of ocular signs to death was 6 or 7 months.³ This was attributed partly to the fact that it takes a long time to diagnose renal carcinoma as the primary lesion in those with initial ocular onset.

Result of treatment modalities for metastatic renal cell carcinoma are still wanting in terms of overall survival benefits. It is believed that a subset of patients with Metastatic Renal Cell Carcinoma and a solitary metastasis (1.6-3.2% of patients) may derive benefit from nephrectomy with resection of the metastatic lesion. A 5-year survival of approximately 35 percent was reported in patients who underwent nephrectomy and surgical resection of a solitary metastasis. This is particularly observed in those with metastatic lesions involving the lung, adrenal gland or brain. Management of orbital metastases, however, has not been addressed in much detail and reports in the literature are wanting.

**References**


CASE REPORT

Incarceration of the Penis by a Metallic Ring

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A 45 year old male consulted at our institution due to penile swelling and pain. A metallic ring was placed around his penis 1 week prior to hospitalization. Emergency management by removal of the iron ring with a bolt cutter was done saving the penis from strangulation. However, due to massive skin loss, skin grafting was done with excellent result.

Key words: penis, metallic ring, strangulation

Introduction

Self-inflicted injury by placement of an iron ring to the penis resulting in incarceration is an uncommon injury. Management requires resuscitation and stabilization of patient with particular attention to psychiatric illness.

There had been several reports on the use of petroleum gel injection, pellets and foreign bodies to enhance the size of the penis causing penile swelling and pain. However, documented case of penile strangulation secondary to metallic ring placement has never been reported locally and it is for this reason that this case is being presented.

Case Report

We are presented with a 45-year old male, known schizophrenic, who was brought to our emergency room because of penile pain and swelling. One week prior to admission, patient intentionally put a metallic ring around his penis for no apparent reason. One day prior to admission, he experienced mild swelling of the glans and penile shaft, however, no consult or medication was taken. The metallic ring was maintained around the penis inspite of the swelling.

One hour prior to admission, increase in severity of the swelling accompanied by severe pain and inability to remove the metallic ring from the penis prompted him to seek consult at our emergency room.

At the emergency room, the patient was conscious, coherent with stable vital signs. On physical examination, a metallic iron ring was found compressing around the swollen mid penile shaft (Figure 1). Examination of the scrotum and both testis were normal. CBC showed leukocytosis. Venoclysis was started and IV antibiotics, anti-tetanus vaccine were given.

He was then immediately brought to the operating room. Intraoperatively, removal of the metallic ring using a bolt cutter (Figure 2) and wound debridement was done (Figures 3 and 5). The penis was salvaged from strangulation but resulted in extensive skin loss. (Figure 4).

Daily wound care was done postoperatively. He was also referred to Psychiatry and started on antipsychotic drugs. He was discharged improved on the 10th postoperative day.
On the 30th postoperative day, he was re-admitted for release of penile skin contracture and split thickness grafting (Figures 6 - 9). The patient tolerated the procedure with excellent results (Figure 10). He was discharged well and improved and advised regular follow up.

Figure 1. Strangulation of penis by metallic ring.

Figure 2. Removal of metallic ring by a bolt cutter.

Figure 3. Penis after removal of metallic ring.

Figure 4. Penis after debridement.

Figure 5. Metallic ring removed from the penis.

Figure 6. Penis after release of contracture.

Figure 7. Skin harvesting from anterior thigh.
Incarceration of the penis with metal rings is a known form of self manipulation to enhance sexual experience.\(^1\) Cases of foreign bodies in the genitourinary tract are always of interest because these occur with such frequency that each urologist and practitioner may expect to treat them.\(^2\) If the incarceration is not relieved, vascular congestion, edema and penile enlargement can result. If left untreated for a prolonged period, ulceration and necrosis can occur. Notably, urinary retention develops only about 50 percent of the time.\(^3\)

The metallic ring may be divided or cut by a file saw or strong cutting forceps. Unfortunately, steel and metal objects are extremely difficult to remove since the hardened industrial material is extremely durable and requires more sophisticated instrumentation such as an air grinder and drills operating at up to 300,000 rpm.\(^4\) If removal of the foreign body is not possible any an of these methods due to the size of the object and extreme degree of edema, the penis may be denuded and postoperative treatment must follow the principles of severe traumatic penile and scrotal avulsion, including skin grafting.\(^5\)

In this case special drills were not available and the maintenance department of the hospital provided us a bolt cutter which was proven effective. After the removal of the metal ring, we proceeded with immediate cleaning and judicious debridement. Daily inspection by the surgical team was done. The use of Foley catheter or suprapubic tube was found to be not necessary since the patient could void spontaneously.

Penile skin defect coverage was done after the patient showed no signs of local infection. Scrotal rotation flaps can be used but these carry the risk of an unacceptable cosmetic result because the scrotum contains hair-bearing skin. Penile skin defect can be managed by flaps from the abdomen and thigh, but they have a less acceptable cosmetic result than split-thickness skin grafting (STSG).\(^6\) A thick graft is better than a thin one because it provides better cosmetic and functional results. Grafts are harvested from the anterior thigh or buttocks.\(^7\)

Split-thickness skin grafting (STSG) was used in this patient. Graft was harvested from the anterior thigh since the use of buttock skin can limit the total length of the graft that can be taken and requires
intraoperative repositioning of the patient from prone to supine position.

Psychologically, the patient appeared stable and cooperative. He was referred to psychiatry and was given appropriate psychotherapy and medication.

References


CASE REPORT

Loss of Vision: An Unusual Manifestation of Prostate Carcinoma

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This is a case of a 69-year old male who presented with gradual loss of vision and protrusion of the right eye because of metastatic prostate carcinoma. Radiologic studies (CT scan and bone scan), PSA and prostate biopsy confirmed the diagnosis. Symptoms were abated after bilateral orchiectomy. Although considered to be unusual, orbital metastasis with its consequent eye involvement can be the presenting symptom of an elderly male with prostate cancer.

Key words: loss of vision, prostate cancer, orchiectomy

Introduction

Prostate cancer usually presents with urinary symptoms in its advanced stage. In most cases, it manifests with symptoms as a consequence of its metastatic nature. Since the bones are the most frequently involved, pain of the affected skeletal structure can be the prominent symptom. The most common sites of bone metastasis, in decreasing incidence, are the spines, ribs, pelvis, femur and shoulder.1-3 Metastasis to the skull is rare and orbital metastasis from prostate cancer is even rarer.2

Nevertheless, the presence of prostate cancer in an elderly male with orbital metastasis with its consequent eye involvement is a possibility.

This paper aims to present loss of vision and other ocular symptoms as an unusual presentation of prostate cancer. It also aims to show the value of proper work-up to come up with the correct diagnosis of metastatic prostate carcinoma and eventual application of appropriate treatment.

Case Report

This is a case of a 69-year old male admitted because of blurring of vision of the right eye.

The patient initially experienced blurring of vision of his right eye accompanied by erythema and painless protrusion. This gradually progressed to complete loss of vision. Examination by an ophthalmologist revealed absence of light perception, prominent proptosis, downward displacement and erythematous conjunctiva of the right eye (Figure 1). Initial laboratory work-up showed anemia and elevated alkaline phosphatase, acid phosphatase and prostate specific antigen (PSA). Other laboratory tests were normal. Bone scan showed multifocal sites of increased tracer accumulation consistent with osteoblastic metastatic disease to the skull (orbital, frontal, maxillary and mandibular bones), shoulder joints, manubrium sterni, left iliac crest, right sacroiliac joint and both distal femoral diaphysis (Figure 2). A cranial computed tomography (CT) scan
showed extensive osteoblastic sclerotic bony changes and metastasis to the orbital cavities, middle cranial fossa and mandible (Figures 3a and 3b). Chest x-ray showed blastic changes of bony structures due to bone metastases (Figure 4). Ultrasound showed bilateral renal cysts and an enlarged, nodular prostate gland. (Figure 5).
Discussion

Most patients with advance prostate malignancy are identified because of symptoms of bladder outlet obstruction and/or findings on rectal palpation. In some cases, a suspicion of prostate malignancy arises because of symptoms from the development of disseminated disease. The most frequently involved organs, in decreasing incidence, are the bones, lungs, liver, pleura and adrenals. Consequently, next to voiding symptoms, the most common manifestation of prostate cancer is due to skeletal involvement.

Evidences suggest the existence of a backward metastatic pathway through veins from the prostate to the spine in addition to classical hematogeneous tumor spread via the vena cava. Prostate cancer has been shown to metastasize by following the venous drainage system through the lower paravertebral plexus, or Batson’s plexus.

Based on the bone scans, the most common sites of spread are the spine (74%, most commonly in the lumbar and thoracic region), ribs (70%), pelvis (60%), femur (44%), and shoulder (41%). The skull is less frequently involved. Even rarer is orbital metastasis which represents only 2 to 9 percent of all adult orbital neoplasms.

Orbital metastasis is rarely symptomatic except perhaps for pain. Uncommonly, it can lead to very distressing and debilitating symptoms. Proptosis and diplopia constitute the most common presenting symptoms of orbital neoplasia. The cranial nerve
deficit can occur from 9 to 102 months with an average of 41.5 months from their initial diagnosis.\textsuperscript{12,13}

It was theorized that visual disturbances due to orbital metastasis developed when the neural-foramina of the optic nerve is compromised by tumor growth or newborn formation.\textsuperscript{10} The mass effect can cause displacement of the involved eye and with ensuing proptosis. Unfortunately, this development is a grave prognostic sign. In a series of 227 cases with carcinomatous metastasis to the eye and orbit, only 1.3 percent (3 cases) had the primary lesion in the prostate gland.\textsuperscript{9} A second series of 28 placed the incidence of a prostate primary at 3.5 percent (1 case).\textsuperscript{8}

Diagnosis of prostatic metastatic disease to the orbit can be suggested by CT scan findings. An orbital mass determined to be hyperostotic, spiculated and osteoblastic on CT with a clinical diagnosis of prostate cancer is highly suggestive of prostatic origin.\textsuperscript{8,11,14,15}

Treatment involves androgen deprivation at several levels along the pituitary-gonadal-axis. Currently, administration of LHRH agonists and orchiectomy are the most common forms of primary androgen blockade used. Treatment involves reducing or alleviating pain as well as maintaining overall neurologic function.\textsuperscript{16}

Irradiation is generally effective in the treatment of distant metastases from carcinoma of the prostate. Patients with skull metastasis experienced marked relief of symptoms in more than 80 percent of cases.\textsuperscript{17}

In our case, the patient experienced marked improvement of the visual acuity and resolution of the proptosis and erythema of the right eye after androgen deprivation.

**Conclusion**

This case illustrates an uncommon case of prostate cancer that metastasized into the retroorbital area and manifested as gradual loss of vision of the right eye. Although considered to be unusual, its occurrence is not remote in view of the predilection of prostate cancer to bone metastasis.

It is therefore appropriate to bear in mind the possibility of prostate carcinoma in any elderly male who presents with gradual loss of vision. Accordingly, prompt and adequate treatment of the primary problem can be addressed. This prudence on the part of the caring physician will not only restore the vision of the patient. More importantly, it can prolong the life of the patient with metastatic prostate cancer.

**References**


Urinary Bladder Exstrophy in a 21-year Old Female

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A case of a 21-year-old female admitted for a hypogastric mass and inability to control her urination since childhood. Physical examination revealed an 8 x 7 cm reddish mass at the hypogastric area with intermittent jet of urine coming out from the inferolateral aspects of the mass. Diagnosis was urinary bladder exstrophy. Intravenous pyelography showed an outpouching mass at the anterior aspect of the pelvis with widening of the symphysis pubis and excretion of contrast medium into both upper urinary tracts but non-filling of contrast medium within the urinary bladder consistent with bladder exstrophy. Cystectomy performed with urinary diversion using the Mainz pouch with an appendiceal stoma and coverage of the abdominal defect with tensor fascia lata myocutaneous flap and rectus femoris muscle flap. On follow-up, patient was continent.

Key words: urinary bladder exstrophy, cystectomy, Mainz pouch, continent

Introduction

Exstrophy of the bladder is part of a spectrum of anomalies involving the urinary tract, the genital tract, the musculoskeletal system, and sometimes the intestinal tract. In classic bladder exstrophy, most anomalies are related to defects of the abdominal wall, bladder, genitalia, pelvic bones, rectum and anus.

Exstrophy of the bladder is rarer and the incidence is calculated to be from 1 per 30,000 to 50,000 live births. It is more frequently noted in males. The male to female ratio of bladder exstrophy is 3:2.1

Bladder exstrophy in adults is rarer and causes difficulties due to upper tract dysfunction and malignant potential. Three cases of bladder exstrophy in adulthood has been reported, one treated with a Kock pouch and 2 adults treated with cystectomy and a modified Mainz pouch.2 There has been one locally reported case of bladder exstrophy in an adult coincident with a uterine myoma.3

The paper aims to present a 21-year-old female diagnosed with bladder exstrophy and treated with cystectomy, continent urinary diversion and flap closure of the abdominal defect.

The paper will also discuss the embryology, prenatal diagnosis, associated anomalies, presentation and treatment of bladder exstrophy.

Case Report

This was a case of a 21-year-old female who consulted for a hypogastric mass and inability to control her urination since childhood. There were no intranatal complicating factors. There was no congenital anomaly among family members. The mother noted the hypogastric mass since birth with continuous flow of urine from the mass. No prior consultation was done and condition was tolerated by wearing diapers. She had regular menstruation since age 13 and has no fecal incontinence.
Physical examination showed normal stance and gait. The abdomen was flat with no visible umbilicus. There was an 8 x 7 cm reddish mass at the hypogastric area with intermittent jet of urine coming out from the lateral aspects of the mass. The mass surrounded bilaterally by pubic hair (Figures 1 and 2).

Diagnosis was Urinary Bladder Exstrophy. Laboratory results were unremarkable. Intravenous pyelography showed wide separation of the symphysis pubis measuring 11 cm with an outpouching mass at the anterior aspect of the pelvis (Figure 3). Excretory urography by intravenous introduction of contrast medium was followed by excretion of contrast medium into both upper urinary tracts with neither filling defect nor dilatation. There was no filling of contrast medium in the urinary bladder. (Figure 4)
Multiple incisional biopsy of the urinary bladder showed Severe Chronic Cystitis Glandularis, with focal superficial ulcerations and extensive epidermidization. The transformed mucosa were lined by well-differentiated, mildly keratinized stratified squamous epithelium with focal ulceration and were disrupted by mucus-producing epithelial cells and glands similar in appearance to colonic mucosa.

Surgical plans were made by the Urology, Plastic surgery and Orthopedic services. The contemplated procedure was to do cystectomy and a continent urinary diversion, then closure of the abdominal defect using flaps. There was no orthopedic intervention contemplated.

Cystectomy with urinary diversion using the Mainz pouch with an appendiceal stoma was performed. The Mainz pouch was derived from the terminal ileum, cecum and portion of the ascending colon (Figure 5). Both ureters were implanted to the pouch. The appendiceal stoma served as the catheterizable stoma. The defect on the anterior abdominal wall created after the removal of the bladder was covered with tensor fascia lata myocutaneous and rectus femoris muscle flaps (Figure 6).

Histopathology showed the excised urinary bladder lined by stratified squamous epithelium exhibiting acanthosis and parakeratosis. The underlying stroma contained several glands lined by mucus-producing intestinal-type epithelium with goblet cells. There was no evidence of malignancy and findings were consistent of an extrophic bladder.

On the 9th postoperative day, pouchgram and bilateral ureterogram showed filling of contrast medium into the pouch and both ureters. There was neither leakage of contrast medium on the anastomotic site nor filling defect on the tract. Volume of contrast medium infused on the pouch was 150 mL (Figures 7, 8 & 9).

Postoperative course was unremarkable. Patient was then instructed on intermittent catheterization of the stoma to evaluate her urine from the pouch. She was discharged well.

Subsequent follow-up revealed patient was continent while on intermittent catheterization. Wound, flaps and stoma were unremarkable (Figure 10).

On the 14th postoperative week, patient was admitted for bilateral flank pains associated with fever and chills. Diagnosis was acute pyelonephritis with pouchitis. She was treated with intravenous antibiotics and discharged improved.
Discussion

The variants of the exstrophy-epispadias complex include bladder exstrophy, cloacal exstrophy, and epispadias. The cause of this complex is thought to be the failure of the cloacal membrane to be reinforced by ingrowth of mesoderm. The cloacal membrane is a bilaminar layer situated at the caudal end of the germinal disc that occupies the infraumbilical abdominal wall. Mesenchymal ingrowth between the ectodermal and endodermal layers of the cloacal membrane results in the formation of the lower abdominal muscles and the pelvic bones. After mesenchymal ingrowth occurs, the urorectal septum grows in a caudal direction and divides the cloaca into a bladder anteriorly and a rectum posteriorly. The cloacal membrane is subject to premature rupture, and depending on the extent of the infraumbilical defect and stage of development during which the rupture occurs, bladder exstrophy, cloacal exstrophy, and epispadias results.4

The international clearinghouse of birth defects noted a slightly increased risk of exstrophy or epispadias in children of mothers less than 20 years of age. Currently, exstrophy of the bladder is relatively rarely diagnosed prenatally. On a retrospective review of 43 prenatal ultrasound studies from 25 pregnancies where the live delivery of an infant with classic bladder exstrophy occurred, the authors were able to make the diagnosis of bladder exstrophy in 67 percent of cases. Only in 13 percent of the patients was the diagnosis of bladder exstrophy made prior to delivery.1

Five criteria associated with bladder exstrophy were identified. (a) A bladder that was never demonstrated on ultrasound. (b) A lower abdominal bulge that represents the exstrophied bladder, which increases in size as the pregnancy progresses and as the intra-abdominal viscera increases in size. (c) A diminutive penis with anteriorly displaced scrotum. (d) A low set umbilical insertion. (e) Abnormal widening of the iliac crests.1 Since the fetal bladder can be seen on prenatal ultrasound after 14 weeks of gestation, the prenatal diagnosis of bladder exstrophy should be entertained anytime the bladder is not demonstrated or if any of the above factors are noted.

Associated anomalies include epispadias, absence of a bladder neck and sphincter, small capacity bladder, abnormally positioned ureters,
separation of the pelvic bones, an anus positioned further forward than usual, low positioned umbilical (belly button), umbilical and inguinal hernia and undescended testes.

The incidence of inguinal hernias in boys with exstrophy ranges from 56 to 82 percent and in girls from 11 to 15 percent. The incidence of incarceration of these hernias in exstrophy patients below 1 year of age was 10 to 53 percent, and therefore it is recommended to repair the hernia at the time of the primary closure.

The diagnosis of classic bladder exstrophy is usually easily made at birth. Characteristically, the bladder plate is seen protruding just beneath the umbilical cord. The rectus muscles are divergent on either side of the bladder, leading to the separated pubic bones. An outward rotation of the innominate bones and eversion of the pubic rami causes this separation.

The male infant exhibits a short epispadiac phallus with a dorsal urethral plate, a splayed glans, and dorsal chordee. The cause of the short phallus is the separation of the pubic bones and there may also be a true deficiency of corporeal tissue. Despite these abnormalities, the penis in bladder exstrophy patients can generally be reconstructed to be cosmetically and functionally acceptable. Inguinal hernias are very common in exstrophy patients due to large internal and external inguinal rings, and lack of obliquity of the inguinal canal.

The anus may be anteriorly placed and fecal continence may be adversely affected by the divergence of the pelvic musculature. Rectal prolapse may occur in untreated patients, but virtually always disappears after bladder closure or cystectomy, and represents an indication for surgical management of the extrophied bladder. In the female, the genital defect is analogous to the male, but more easily reconstructed. The mons pubis, both hemiclitori and labia are separated and the vaginal orifice is displaced anteriorly. The pelvic floor defect predisposes to uterine prolapse, especially after pregnancy and delivery.

Management of bladder exstrophy is best started in the neonatal period. In infancy primary reconstruction is increasingly performed with good results. At birth, the umbilical cord should be ligated with suture to avoid bladder mucosal damage that can be caused by an umbilical clamp. The bladder is best protected with clear plastic wrap and each time the diaper is changed the bladder surface should be irrigated with sterile saline and the wrap replaced.

The urinary tract should be investigated with ultrasound or a radionuclide scan to assess overall function.

Closure of the pelvic ring is of great importance for the initial closure and to the eventual attainment of urinary continence. When the initial closure is carried out within the first 72 hours of life, while the newborn is still under the affect of the maternal hormone relaxin, the pelvic ring can sometimes be closed effectively without the need for osteotomy. However, when the pubic separation is wide, or the surgery is performed at an older age, or at the time of reclosure (after a prior closure failed), osteotomy is essential to achieve good closure of the pelvic ring. The osteotomy should be performed at the same time of the bladder closure, as it reduces the tension on the suture lines and secures the closure. In addition, the osteotomy helps to restore the pelvic anatomy and thus increase the chances of eventual continence and reduce the likelihood of uterine prolapse.

The factors which are important for achieving successful primary closure have been well documented. These include use of osteotomy, avoidance of urethral tubes and abdominal distention, the use of postoperative antibiotics, pelvic immobilization, urethral stenting catheters, and maintenance of the patient free of pain. An intravenous pyelogram (IVP) is obtained to assess the status of the upper tracts and catheterization is performed to obtain residual urine and urine culture. If the initial IVP shows good drainage, the upper tracts are followed with ultrasound every 6-12 months. Prophylactic antibiotics are usually continued for several years. In cases of upper tract dilatation and high residual urine, urethral dilatation or intermittent catheterization may be necessary.

Not all exstrophy patients will be candidates for functional reconstruction, usually because of very small bladder plates or hydronephrosis. Continent diversion is appropriate for children whose bladders are unsuitable for functional reconstruction.

The goals of continent diversion should include adequate storage of urine under low pressure, ability to empty the reservoir periodically and a satisfactory cosmetic appearance to promote positive self-image.

For those patients living in third world countries, and areas where sanitary conditions and medical attention are not readily available, intermittent catheterization can be problematic due to a lack of running water and disposable catheters. Likewise, in those patients who are unwilling to accept
intermittent catheterization a simple maintenance-free form of urinary diversion provides obvious advantages.5

Bladder exstrophy is extremely rare in adulthood because definitive treatment with primary reconstruction is possible in infancy. When untreated, this condition has malignant potential. Cystectomy and urinary diversion are recommended because the bladder plate is thick, scarred and inflamed by long-standing irritation.

Ileal conduit urinary diversion was initially felt to be ideally suited to exstrophy patients, however, studies revealed significant long term complications. The non-refluxing colon conduit urinary diversion seems to achieve better long-term results than ileal conduits.

During the last 2 decades, several different techniques have been developed to create continent catheterizable conduits including Mitrofanoff, Benchekroun and Indiana stomas, and servomechanical sphincter. Each method has potential advantages and disadvantages. The use of the appendix has become popular because after implantation into the low pressure reservoir in a non-refluxing fashion it allows for easy catheterization with a low overall complication rate. The excellent blood supply of the appendix allows it to be manipulated without unduly risking stomal ischemia, and the narrow lumen of the appendix has an extra advantage in facilitating catheterization by preventing inadvertent looping of the catheter.6

Review of the clinical experience with the Mitrofanoff principle catheterizable continent urinary diversion showed that it is easily performed, successful and a very valuable adjunct in the reconstruction of the bladder in children.7

Bladder exstrophy patients achieve good results regarding continence. Sexual function is fair in the male patient and good in the female patient, and psychosocial integration appears to be adequate. However, fertility in most of the male patients is in doubt and psychosexual developmental issues may be more of a problem for men than for women. With current refinements in the treatment of bladder exstrophy and male infertility, the results are expected to improve in the future. The long-term results in exstrophy patients, other than male infertility, are acceptable. Therefore, when exstrophy is diagnosed prenatally, the parents can be reassured that the long-term outcome for these children is optimistic.

References
Laparoscopic Adrenalectomy: A Surgical Option for the Management of Cushing’s Syndrome in Adrenal Adenoma

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Cushing’s syndrome from primary adrenal gland malfunction is most commonly caused by a solitary adrenal adenoma. Complete surgical excision as the standard treatment has evolved from the conventional anterior abdominal laparotomy or a flank approach to the laparoscopic, minimally invasive resection. Laparoscopic surgery offers lower intra-operative blood loss, minimal post-operative pain and shorter hospitalization. We report a 21-year old female with Cushing’s syndrome who underwent laparoscopic resection of a right adrenal adenoma. Our limited experience has taught us that with proper patient selection, laparoscopic adrenalectomy is a safe and very promising management option.

Key words: laparoscopic adrenalectomy, Cushing’s syndrome, adrenal adenoma

Introduction

Hypercortisolism is a rare consequence of adrenal malfunction estimated to have an annual incidence of 10 per million population. In 1932, Harvey Cushing described eight patients with truncal obesity, hypertension, fatigability, weakness, amenorrhea, hirsutism, abdominal striae, edema, glucosuria and osteoporosis. This constellation of signs and symptoms is now known as Cushing’s syndrome. Approximately 10 percent of cases of endogenous hypercortisolism is a result of a primary adrenal abnormality. The most common is a solitary adrenal adenoma that secretes cortisol independent of ACTH control. The goal of therapy is to eliminate cortisol hypersecretion by total surgical excision is the treatment of choice.

The development of laparoscopic technique has evoked great enthusiasm for minimally invasive surgical procedures. Adrenalectomy is no exception. Advantages appear to include decreased post-operative pain, shorter post-operative rehabilitation period and better cosmesis. This case provides preliminary data that, in carefully selected patients, laparoscopic adrenalectomy maybe considered as a good alternative to an open surgical approach.

Case Report

This was a case of a 21-year-old female patient who was admitted at Far Eastern University – Dr. Nicanor Reyes Medical Center (FEU-NRMF MC) in June 28, 2001, with a diagnosis of Cushing’s syndrome secondary to a cortisol secreting right adrenal mass.

Two and a half years prior to admission, the patient observed swelling of the face and fat deposition on the supraclavicular and suprascapular areas. A year prior to admission, she noted abundant growth of facial hair and later developed irregular menses. Plasma cortisol was elevated and ACTH level was 10 pg/ml. Abdominal CT scan revealed 2.7 x 2.3 x 2.1 cm suprarenal mass. Pertinent physical examination findings were moon facies with thinning of facial skin, abundant facial hair and fat deposition along the supraclavicular and suprascapular areas. Multiple striae were also noted on her chest, axilla, abdomen and proximal extremities.
Laboratory examinations revealed a persistently elevated 24-hour urine free cortisol (132-316 ug/24h) and no suppression was noted with Dexamethasone administration. She was admitted for surgical intervention and underwent laparoscopic right adrenalectomy on the second hospital day. Hydrocortisone 100 mg IV bolus was given an hour prior to surgery. A 3.5 x 2.5 x 1.7 cm adrenal adenoma was removed. Patient was maintained on Hydrocortisone drip at 100 mg every 24 hours postoperatively. She remained stable with an uneventful postoperative course. Hydrocortisone was shifted to oral Prednisone 15 mg daily on the 3rd day and the patient was discharged on the 4th postoperative day.

Operative Technique

The principles of laparoscopic adrenalectomy are very similar with those of the open anterior approach.

Discussion

Cushing’s syndrome is a clinical disorder caused by overproduction of cortisol. Adrenal adenoma is the cause in 5 percent of cases. With the exception of adrenal carcinomas with sizes ranging from >8-10 cm which are likely to be locally invasive and are best approached by a traditional abdominal or flank incision, virtually all adenomas and small adrenal carcinomas maybe removed laparoscopically. It is safe and requires a shorter postoperative hospital stay. There is also lower intraoperative blood loss and less analgesic requirement. The smaller incisions offer a more aesthetic wound which are less painful. The transabdominal laparoscopic approach has the advantage of providing a large intraabdominal working space. Hemorrhage from tearing the adrenal vein is one of the most significant and potentially life threatening complications of surgical resection especially in the right where the adrenal
vein is short and drains directly into the inferior vena cava. This appears to be another advantage of the laparoscopic approach which provides a better and early access to adrenal vessels prior to dissection.

Patients with adrenal tumors causing Cushing's syndrome must receive glucocorticoids post-operatively. Daily hydrocortisone is usually maintained at 12-15mg/m^2 and maybe withheld after a normal response to ACTH stimulation test.

No complications were observed in our patient. She had her latest follow-up 15 months post-operation and moon facie has resolved. Central obesity has regressed and hirsutism was absent.

References


