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Case Report

Bladder diverticuli following injection of onabotulinum toxin A in a patient with multiple sclerosis and autosomal dominant polycystic kidney disease

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ABSTRACT

Urinary incontinence due to neurogenic detrusor overactivity is common in patients with disorders of lower motor neurons controlling the bladder. Multiple sclerosis is a major cause of neurogenic detrusor overactivity, which negatively impacts quality of life. Bladder wall injection of onabotulinum toxin A can diminish spontaneous bladder contraction, urinary urgency, and urge incontinence. Herein we report a 61-year-old woman with multiple sclerosis and autosomal dominant polycystic kidney disease with bladder trabeculation developing after repeated injections of onabotulinum toxin A.

1. Introduction

Botulinum toxin treatment of overactive bladder is effective for patients who have failed conservative treatment and it has been approved for this indication by the Food and Drug Administration [1–3]. A recent meta-analysis by Drake et al indicated that 12 weeks of intravesicular injection of botulinum toxin (100 U) provides greater relief of overactive bladder symptoms than oral or transdermal anticholinergics, or mirabegron, a beta$_3$-receptor agonist [4]. Adverse effects of onabotulinum toxin A treatment include acute urinary retention (8.9%) [5], postoperative urinary tract infection (21.1%) [1], muscle weakness (2%-12%) [6], and autonomic dysfunction [7]. Hematuria (macroscopic) and bladder clots have also been reported in multiple studies [5,8].

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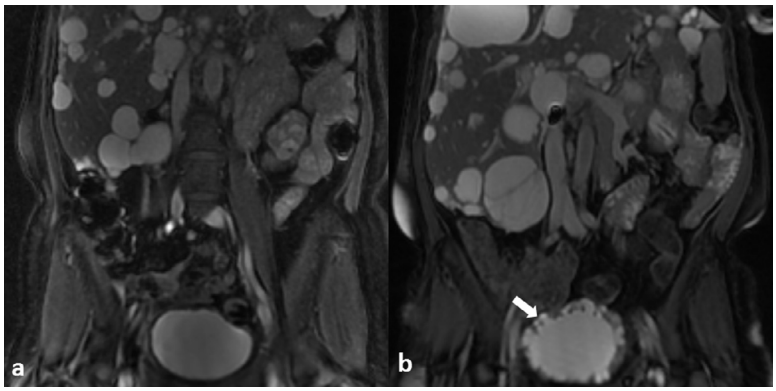

Fig. 1 – Coronal SSFP MRI of the bladder (a) prior to botox injection and (b) at presentation 3 months post the second bladder botox injection. Note the increased bladder wall thickness (solid white arrow) with multiple cyst-like diverticuli and thick trabeculations. Also note multiple cysts enlarging the liver (open white arrow) related to her ADPKD.

Table 1 – Bladder wall thickness and dimensions values at 3 time points.

Date of scan	Bladder wall thickness (mm)	Bladder wall dimensions (mm)	Number of diverticuli
2012	3.9	89.6 × 62.0	0
2014	4.5	97.5 × 52.8	1
2017	10.9	106.8 × 76.0	18

Table 2 – Laboratory results prior to botox injection and at presentation 3 months post the second bladder botox injection.

	Pretreatment (2013)	Posttreatment (2017)
Serum creatinine (mg/dL)	1.28	1.57
BUN (mg/dL)	21	40
BUN/creatinine ratio (ratio)	16	26
eGFR (mL/min/1.73 m^2)	43	33
Urine protein	23.9	91.2
Postvoidal residual volume (mL)	120	480

BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate.

2. Case report

A 61-year-old woman with multiple sclerosis (MS) and autosomal dominant polycystic kidney disease (ADPKD) underwent magnetic resonance imaging (MRI) abdomen and pelvis as part of her ongoing participation in The Rogosin Institute ADPKD Repository, a longitudinal observational study that includes biennial MRI [9]. She was diagnosed with MS approximately at the age of 35 years. Her urologic complications include overactive bladder with urge incontinence. Approximately at the age of 54 years, she was found to have a large postvoid residual volume (PVR). Prophylactic hexamethylenetetramine (Hiprex) effectively prevented urinary tract infection. Therefore an indwelling bladder catheter was not required.

Protocol MRI scans in 2012 and 2014 (Fig. 1) showed mild bladder trabeculation but no bladder diverticuli. The PVR was 120 mL prior to treatment with onabotulinum toxin A (Table 1).

In August 10, 2016, using cystoscopic guidance, a total of 200 units of onabotulinum toxin A (Botox) was reconstituted in 20 mL of sterile saline and injected in the detrusor muscle in 20 different locations in the posterior and lateral walls of the bladder (1.0 mL per location). The indications were lower urinary tract symptoms, including increasing urinary urgency and frequency. A follow-up injection of a total 200 units, using the same treatment protocol, was performed on February 8, 2017 (Fig. 2, Table 2).

There was symptomatic improvement in urinary urgency following onabotulinum toxin A treatment despite persistent elevated PVRs ~500 mL and 410 mL 1 and 2 months after each treatment, respectively.

A follow-up, protocol MRI of the abdomen in May 2017, 9 months after the first injection, and 3 months after the second injection of onabotulinum toxin A, showed interim development of severe bladder trabeculation and multiple bladder diverticuli. Hexamethylenetetramine was discontinued in response to the progression of her chronic kidney disease (Table 1).

After the MRI, a follow-up cystourethroscopy showed marked trabeculations and scattered diverticula throughout the urinary bladder confirming the MRI observations. These findings represent a change when compared with the cystoscopic findings 6 months prior and confirm the MRI findings.

3. Discussion

The novel findings observed by steady state free precession (SSFP) MRI images in this case are the development of severe

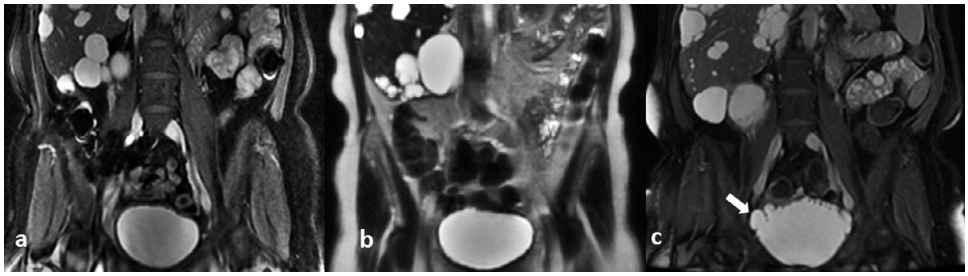

Fig. 2 – Coronal SSFP MRI of the bladder at 3 time points (a) 2012, (b) 2014, and (c) 2017 after botox injection of bladder wall. Arrow points toward hutch diverticulum.

bladder trabeculations and diverticuli, with intervening regions of thinned bladder wall following onabotulinum toxin A injections into the bladder wall. Bladder trabeculation is characterized by morphological and histological changes due to hypertrophy and hyperplasia of the bladder muscle and infiltration of the connective tissue [10]. These result from bladder distention, outflow obstruction, and uninhibited detrusor contractions. In view of focal bladder wall paralysis caused by onabotulinum A injections, the possibility that diverticuli are developing at the site of these injections should be considered. A search of our hospital radiology Picture Archival Computer System including over 3000 pelvic MRI scans was performed. No comparable cases of bladder wall hypertrophy with diverticuli were identified.

Although both Single Shot Fast Spin Echo (SSFSE) and SSFP pulse sequences are T2 weighted, showing contrast between the T2 bright urine and T2 dark muscular bladder wall, SSFP showed the trabeculation and diverticuli with greater clarity. This is partly due to the higher signal-to-noise efficiency of SSFP, which allows for thinner slices with higher matrices. SSFP also emphasizes the border between muscle and urine, allowing better image contrast. Future studies investigating this phenomenon should incorporate the SSFP MRI pulse sequence.

Bladder diverticuli and trabeculations with intervening regions of thinned bladder are not likely to be a primary manifestation of ADPKD. The bladder wall changes in this patient were most likely to be related to treatment with onabotulinum toxin A, although there is limited information regarding the bladder wall changes following treatment in MS patients. Alternatively, these bladder changes might have been caused by the chronic bladder dilatation, although this was not found during a retrospective review of MRI scans of other patients at our medical center. The mean duration of clinical response observed in MS patients was reportedly 9.4 months [11]. However, it is unclear whether significant regression of the marked bladder wall changes will occur during this period.

In randomized clinical trials, adverse events following anbotulinum toxin A bladder injection included the significantly increased incidence of urinary retention requiring intermittent bladder catheterization [1,5]. Injection of botulinum toxin at multiple sites along the bladder wall reduces bladder overactivity, increases cystometric and maximum bladder capacity, decreases voiding pressure, and decreases urinary incontinence that is caused by detrusor overactivity [1]. This patient had subjective clinical improvement in lower urinary tract symptoms after treatment that has been sustained for more than 6 months and did not require intermittent bladder catheterization.

The incidence of urinary tract infection increases in MS patients who develop urinary retention after botulinum toxin treatment. This has been attributed to the increased requirement for intermittent bladder catheterization. However, the numerous bladder wall diverticuli observed in this patient provide sites of urinary stasis potentially allowing bacterial growth that cannot be cleared normally. This is of particular concern for ADPKD patients, who are at risk for kidney cyst infection, which is challenging to diagnose and treat.

4. Summary

We identified a patient with ADPKD and MS who developed bladder trabeculations and diverticuli, with intervening regions of thinned bladder following treatment with onabotulinum toxin A for neurogenic overactive bladder.

Compliance with ethical standards

Funding: No

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Disclosure of potential conflicts of interest

Syed Imran Raza declares that he has no conflict of interest.
Ashkan Heshmatzadeh Behzadi declares that he has no conflict of interest.
Jon D. Blumenfeld declares that he has no conflict of interest.
Sarah K. Girardi declares that she has no conflict of interest.

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