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CASE REPORT

Does this case hold the answer to one of the worse types of pain in medicine—that of loin pain haematuria syndrome (LPHS)

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Summary

A patient with loin pain haematuria syndrome suffering chronic throbbing pulsing pain overlaid with prolonged periods of incapacitating colic and overnight vomiting was presented 10 months following diagnosis. Ultrasound was normal. No renal or ureteral stones, or filling defects were seen on CT. At cytoscopy, bladder and urethra were normal, and bloody urine effluxed from the left ureteric orifice. The ureters were normal at diagnosis, and developed new abutting non-penetrating calcifications by 8 months. Pain episodes of complete incapacitating intensity of 2–4 h duration were reduced to 10 min with 5 mg crushed tadalafil administered at onset. If tadalafil was delayed to after onset, the original course of agony resulted. Daily tadalafil reduced loin pain intensity, but not the exacerbations. Tadalafil efficacy may indicate that the pain exacerbations are due to spasm of ureter smooth muscle. 5 mg tadalafil taken at onset alleviated severe loin pain exacerbations in this case of loin pain haematuria syndrome.

Background

Haematuria accompanied by repeated prolonged bouts of colicky pain in the absence of any other pathologies associated with the urogenital system, is termed classical loin pain haematuria syndrome (LPHS).1–3 It is rare (0.12/1000) but the pain can be considered to be among the worst that can be experienced and is profoundly disabling. The haematuria is glomerular in origin,4 can be witnessed with or without clots, and can be detectable by microscopy between episodes. The pain can be unilateral or bilateral, resistant to standard analgaesia as well as, eventually, to opiates, and can be of such severity as to warrant nephrectomy or renal autotransplant with denervation. Pain alleviation has recently been reported after bilateral splanchnic nerve ablation.5 It is reported that renal denervation gives prompt relief but haematuria and pain can recur in the contralateral side. Periods of pain may or may not occur coincidental to periods of frank haematuria. Haematuria is

controlled by ACE inhibition.3 We describe the use of the phosphodiesterase-V (PDE-V) inhibitor tadalafil to reduce the severity of the ureteral tetanus in a patient with LPHS, leading to a significant improvement in quality of life.

Case presentation

A 35-year-old woman was referred to the Brampton Pain Clinic with LPHS for consideration of narcotic pain relief. Ramipril had been prescribed, which reduced the frequency of haematuria, but not the frequency of loin pain. She presented with haematuria, a permanent throbbing pulsing pain overlaid with prolonged periods of very severe colicky pain of 2–4 h duration followed by severe ache that were paralysing in severity, highly intrusive, and had been occurring for the previous 10 months. Nightly vomiting due to the pain was reported.

Social history contained no stressors. She was well balanced and exhibited frustration at being unable to work. As a direct result of the pain the patient's functional capacity was severely limited: she had ceased employment as a busy senior business executive, and stopped her graduate studies and volunteer work, and had heavily restricted daily living activities.

The patient had suffered endometriosis for many years with numerous treatments and became pain free after hysterectomy with bilateral salpingo-oophorectomy until the sudden onset of the above symptoms 7 months later.

Investigations

Physical examination found her to be thin, with a body mass of 41 kg, reduced from her usual slight weight of 54 kg. No evidence of fibromyalgia was found. Pain tolerance using a Fischer Probe was normal. Blood pressure (BP) 110/70 mm Hg. Abdomen was normal except for mild tenderness over the line of left ureter and renal angle, with definite cutaneous hypersensitivity over this area.

Ultrasound revealed normal sized kidneys and no evidence of diffuse or focal disease. 3 mm axial CT images using renal colic protocol followed by contrast-enhanced images and delayed images through the collecting system were taken. There were no stones, no lesions intrinsic to the ureters, the bladder was unremarkable, no hydronephrosis and no adenopathy. No filling defects in the intrarenal collecting system or ureters were seen. Cytoscopy revealed an unremarkable bladder and urethra, including the trigone. Bloody urine was seen effluxing from the left ureteric orifice. LPHS was diagnosed. Eight months after diagnosis, new calcifications developed that abutted the side wall of the left ureter but did not penetrate the ureter itself.

Differential diagnosis

The pain was broken down into a number of patterns.

First there was a diffuse generalised body pain associated with a decrease in pain threshold; it appeared to be increasing after every severe attack. Next there was an intermittent left

renal angle pain, a dull ache made worse on movement or when riding in a car, associated with skin hypersensitivity over the renal angle. Finally, left loin pain radiated into the groin and urethra with severe spasms building up into a continuous tetanic pain that caused the patient to adopt a fetal position on the floor for 2–4 h. These latter pains followed the classical distribution for ureteral pain, under the ribs, following the line of the ureter down to the loin indicated ureteral origin.

The diagnosis that the extreme exacerbating spasms were following the pattern of ureteral pain suggested that a ureteral smooth muscle relaxant might provide relief.

Treatment

With the use of ramipril and non-narcotics in large doses having failed (acetaminophen plus codeine 30 mg), the patient was started on extended release oxycodone from 5 to 10 mg two times per day. Following reports that PDE-V inhibitors such as tadalafil6 relax the bladder neck and accompanying pain, and after considerable discussion with both the multidisciplinary team and the patient, the patient was started on off-label, crushed tadalafil 5 mg given at the attacks of ureteric loin pain.

Outcome and follow-up

Initial therapy with ramipril reduced the haematuria and with baseline pain relief (oxycodone 20 mg) gave a mild blunting of the permanent pain. This permitted the resumption of very basic social functions such as present wrapping at Christmas. However, the paralysing ureteral exacerbations continued. The first dose of crushed tadalafil 5 mg, taken at pain peak, resulted in complete cessation of each and every pain exacerbation within 4–7 min, especially if powdered. In addition, the chronic pain was attenuated. Following concern of the team regarding the hypotensive actions of tadalafil, BP was monitored at the onset of exacerbations and after tadalafil. At the onset of exacerbation, BP was recorded at 98/56, heart rate 86 bpm, increasing to 107/70, 99 bpm, at cessation of pain 3 min after tadalafil. Normal BP was 83/42 and heart rate 76 bpm.

Removal of oxycodone baseline pain medication resulted in the disabling chronic throbbing pain returning within 4 days, but the exacerbations continued to be controlled by acute administration of tadalafil. Replacement of acute symptomatic administration of tadalafil with chronic administration 5 mg/day resulted in a prolonged breakthrough 7 h ureteral spasm. Unlike all previous occasions where the spasms responded, this was resistant to a further 5 mg given at its onset. Because of the severity of the breakthrough spasm, the tachyphylaxis to further tadalafil, and reduced BP with dizziness at standing and at rest, this approach was stopped and the baseline pain control with oxycodone was restored.

The patient's background pain is controlled with long-acting oxycodone, which is being tapered from 20 mg. Spasms are controlled with 5 mg powdered tadalafil taken at spasm onset.

Discussion

The extreme pain suffered in LPHS has resulted in desperate and invasive measures to alleviate the pain. This case was no exception, with the patient considering renal denervation. The differentiation between chronic and acute exacerbations permitted the diagnosis that the latter were due to ureteric tetanus, and possibly associated with ischaemia with resulting calcification, and permitted the consideration of a PDE-V inhibitor to both relax the ureter and improve ureter blood perfusion. The immediate administration of tadalafil in a rapidly absorbable form at the onset of exacerbations alleviated the intense pain. Concerns regarding the hypotensive episodes did not transpire, likely due to the sympathetic response to the pain.

The upper urinary tract is innervated by peptidergic and autonomic neurones, and activation induces ureteral peristalsis through neuropeptides, tachykinins, norepinephrine and acetylcholine. Activity originates in the renal calyx, to stimulate afferent and collateral nerves,7 and can induce retrograde peristalsis, which is very likely to be extremely painful. The onset of pain in LPHS and the episodes of ureteral tetanus is reported to be preceded by one or more episodes of haematuria. However, once established, these episodes may occur in the absence of visible blood, but haematuria can be detected by cytology in between. The coagulation status of blood in the haematuria is unknown, however, clots have been reported.2 ,3 If the coagulation cascade is activated, with or without clot disruption, the activation of the complement and plasma protein cascades as well as platelets would release potent mediators such as C3a, C5a, kinins and thromboxane, for which the ureter possesses receptors, and may contract chronically in response.8 ,9 Indeed, it may be hypothesised that these factors may synergise to produce a tetanic state.

The human ureter expresses PDE-V,7 and its inhibition induces ureteral relaxation.10 This is through the accumulation of cyclic guanosine monophosphate (cGMP), which activates protein kinases and calcium channels, which results in the reduction in cytosolic calcium leading to muscle relaxation. This mechanism operates in human ureteral smooth muscle with PDE-V inhibitors sildenafil, tadalafil and vardenafil relaxing ureters precontracted with potassium or acetylcholine, and accompanied by enhanced accumulation of cGMP.11 ,12 The antagonism of ureteral contraction induced by the other mediators remains to be reported.

An additional or alternative mechanism by which tadalafil might act is through reversal of transient intrarenal vasospasm, which has been observed by Bergroth and coworkers in two of four women with LPHS.13

The use of tadalafil in this patient has resulted in the alleviation of pain in LPHS, and could be the first step towards the non-invasive treatment of the intractable opiate insensitive pain of this syndrome. Although not total, this has had a dramatic impact on this patient's well-being.

In LPHS, baseline pain management will require individualised management. The diagnosis of acute incapacitating colic pain due to ureteral tetanus may be managed by tadalafil or other PDE-V inhibitors. As the ureteral pain is controlled, baseline pain may be managed with reduced analgaesia.

The logical next step, if tadalafil ever fails, is to consider other agents acting via the nitric oxide/cGMP pathway such as nitrogen donors, perhaps administered as angina sprays.

Patient's perspective

- The worst part of loin pain haematuria syndrome is the urinary spasms. The best way to describe them is to compare them to attempting to pass multiple large kidney stones while in active hard labour. They're completely debilitating, they cause me to collapse, and I can't so much as turn my own head. They're seemingly random, hitting whenever and wherever. They would last four, sometimes even 6 h straight. Sometimes with no more than a ten minute break between pulses. I quickly lost the active lifestyle I'd grown accustomed to, and I was ready to give up. Before using tadalafil, I'd been known to hit my head while writhing, and when I was fortunate enough to have it end, the lingering agony would leave me bedridden for weeks. Now, I have my hope back. Within 12 minutes the spasm is gone, leaving the pain a distant, foggy memory. I'm slowly getting my life back. I'm even directing a cast of 35 in a production of *Alice in Wonderland*. Recently, I've even noticed that I can now generally feel the spasm coming on, albeit briefly, which will allow me more of my old life back. Most importantly, my daughter and my husband no longer see me in the pain they did before. Tadalafil, and adequate pain management, have given me my hope, a hope I never thought possible last year, when I really wanted to give up, so that the pain would just finally stop.

Learning points

- Loin pain haematuria syndrome is catastrophically debilitating.
- Loin pain may be broken down into components to clarify, guide and focus pain management.
- Baseline pain requires individualised management and titration. As the acute attacks are controlled the pain threshold improves allowing reduction of background analgaesia.
- Ureteral exacerbations may be managed by the phosphodiesterase-V inhibitor tadalafil administered at onset in a rapidly absorbable form.
- Chronic administration has greatly reduced effectiveness.

References

1. Little PJ, Soper JS, de Wardener HE. *A syndrome of loin pain and haematuria associated with disease of renal peripheral arteries. Q J Med 1967;36:253–9.*
2. Taba Taba Vakili S, Alam T, Sollinger H. *Loin pain hematuria syndrome. Am J Kidney Dis 2014;64:460–72.*
3. Herbert LA, Bendetti C, Parikh SV, et al. *Loin Pain Hematuria syndrome. Uptodate 2014. http://www.uptodate.com/contents/loin-pain-hematuria-syndrome.*
4. Spetie DN, Nadasdy T, Nadasdy G, et al*. Proposed pathogenesis of idiopathic loin pain-hematuria syndrome. Am J Kidney Dis 2008;47:419–27.*

5. Moeschler S, Hoezler BC, Eldridge JS*. A patient with loin pain haematuria syndrome and chronic flank pain treated with pulsed radiofrequency of the splanchnic nerves. Clin J Pain 2013;29:e26–9.*
6. McVary KT, Roehrborn CG, Kaminetsky JC, et al*. Tadalafil relieves lower urinary tract symptoms secondary to benign prostatic hyperplasia. J Urol 2007;177:1401–7.*
7. Fry C*. Pharmacology of the urinary tract. Surgery 2008;26:141–4.*
8. Zahedi R, Braun M, Wetsel RA, et al*. The C5a receptor is expressed by human renal proximal tubular epithelial cells. Clin Exp Immunol 2000;121:226–33.*
9. Ribeiro AS, Fernandes VS, Martínez MP, et al*. Pre- and post-junctional bradykinin B2 receptors regulate smooth muscle tension to the pig intravesical ureter. Neurol Urodyn 2014. doi:10.1002/nau.22685[Epub ahead of print.*
10. Taher A, Schulz-Knappe P, Meyer M, et al*. Characterization of cyclic nucleotide phosphodiesterase isoenzymes in the human ureter and their functional role in vitro. World J Urol 1994;12:286–91.*
11. Kuhn R, Uckert S, Stief CG, et al. *Relaxation of human ureteral smooth muscle in vitro by modulation of cyclic nucleotide dependent pathways. Urol Res 2000;28:110–15.*
12. Gratzke C, Ückert S, Kedia G, et al. . *In vitro effects of PDE5 inhibitors sildenafil, vardenafil and tadalafil on isolated human ureteral smooth muscle: a basic research approach. Urol Res 2007;35:49–54.*
13. Bergroth V, Konttinen YT, Nordström D, et al*. Loin pain and haematuria syndrome: possible association with intrarenal arterial spasms. BMJ (Clin Res Ed) 1987;294:1657.*