

Deflux complications

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Objectives: To report the details of three cases presenting with complications after the injection of Deflux for vesicoureteral reflux (VUR) management and to review the literature on potential long-term adverse events.

Patients and methods: Three patients presented after Deflux injection. Two had persistent VUR and infections, the third had a later diagnosis of irritative bladder symptoms and calcified mounds at the level of the distal ureter. Their cases and the literature were reviewed for complications related to the endoscopic injection technique.

Results: In two patients, the Deflux injection mounds did not produce an antireflux configuration of the ureteral orifice, and both patients had significant fibrosis at reoperation. Histological examination of one patient showed giant cells, inflammatory changes, persistent carrier substance (hyaluronic acid), and calcification. The third patient presented with irritative bladder symptoms and had two calcified mounds, one adjacent to each ureteral orifice.

Conclusion: Deflux injection may be associated with the prolonged persistence of the carrier substance, leading to chronic inflammatory changes and potentially long-term calcification, with uncertain implications. Late calcification is supported by the literature review.

Keywords: Deflux complications, management, vesicoureteral reflux

Introduction

While the debate over the role of surgery in vesicoureteral reflux (VUR) management remains unresolved, endoscopic injection of dextranomer microspheres (Deflux) has become commonplace since its approval by the United States Food and Drug Administration (FDA).^{1,2} Deflux has largely replaced the use of Teflon and silicone, which were the initial agents used for the endoscopic VUR management, mainly due to concerns about Teflon and silicone particle migration.³⁻⁵ Since its first use, Deflux has been effective because it changes the configuration of the ureteral orifice, and an inflammatory response to the injected dextranomer microspheres develops. Some loss of the volume of the mound is expected because of the assumed absorption of the carrier substance, hyaluronic acid.²

Few publications report the macroscopic and histological findings of open surgery after failed Deflux cases.⁶ Contraindications to the substance's use should also be further evaluated.⁶ Additionally, the importance of ultrasound observation of the postoperative collection of Deflux, to confirm the appropriate position and its persistence, has not been recognised, and the development of calcification has not been extensively studied, with 2–10% calcification rates.^{6,7} Previous case reports documented incidental observations of calcification, which should be considered; however, cases of late-presentation calcific lesions and obstruction have been recorded.⁸⁻¹¹

Patients and results

All three cases have been included after written parental consent for the inclusion of deidentified material.

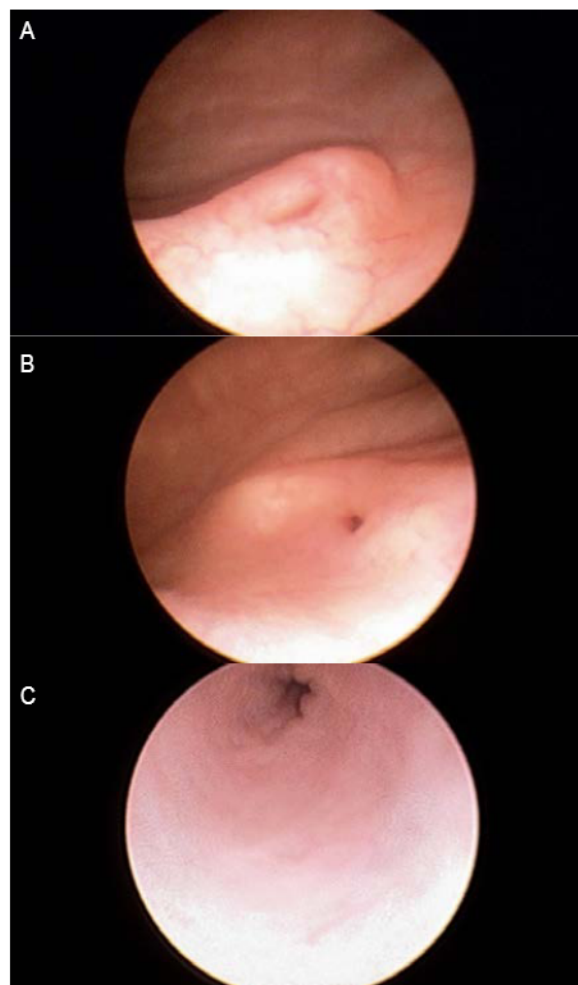


Figure 1: A – a mound of Deflux paste cranial and lateral to the left ureteral orifice at 2 o'clock, B – one of the three Deflux mounds evident above and lateral to the open ureteral orifice that the cystoscope could easily enter (seen in C, the view of inside the ureter).

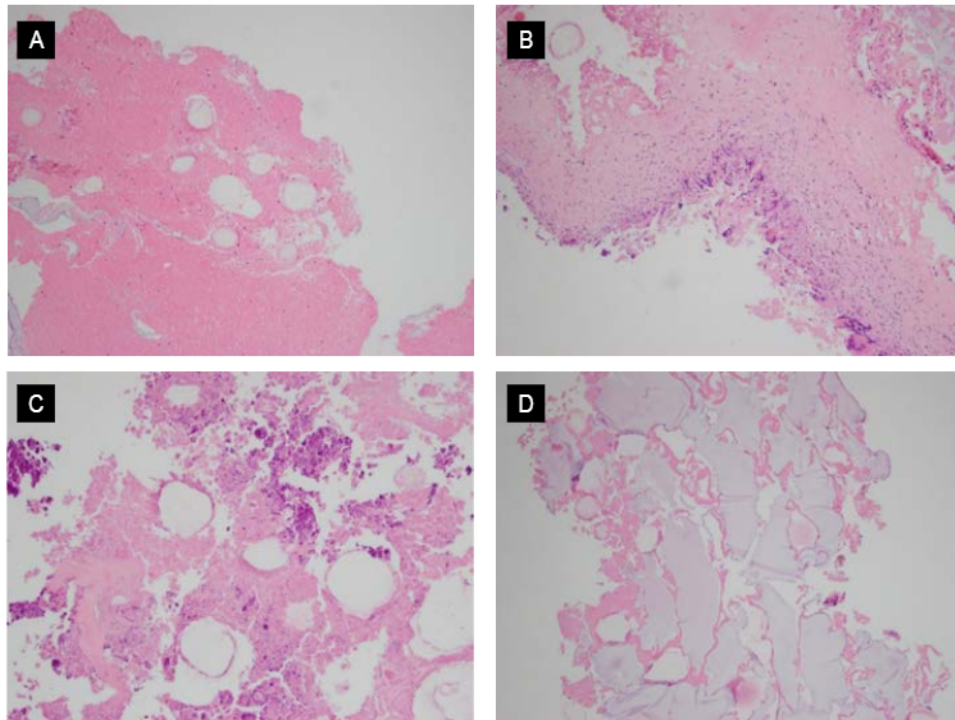


Figure 2: A – dextranomer microspheres within inflammatory tissue, B – the associated foreign body giant cells, C – dystrophic calcification near dextranomer microspheres, D – the pale purple collection is the staining of hyaluronic acid

Case 1

In case 1, a girl presented to the clinic at age four with recurrent urine infections. Deflux was injected for VUR management when she was two years old. A total of 1.0 ml of Deflux paste was injected, with the larger amount on the right side (the initial treating surgeon did not record the exact proportions). Reflux nephropathy changes were present on a mercaptoacetyl triglycine (MAG3) nuclear medicine study, with 29% overall function on the right.

Subsequently, the child had recurrent febrile urinary infections. The Deflux mounds were not visible on ultrasound, and she underwent further cystoscopy. The right orifice could allow passage of a 9.5 French scope, with the Deflux appearing to be in three separate locations around the orifice, and a small amount of paste was cranial and medial to the left orifice. Figure 1 shows the open right ureteral orifice and minimal paste that was mainly cranial and lateral to the right ureteral orifice, and the Deflux adjacent to the left orifice.

The patient's left kidney was normal on ultrasound, and the right kidney was small and scarred, consistent with the MAG3 nuclear medicine study that showed 29% of overall renal function on the right. Persistent VUR was seen on the indirect radionuclide cystogram.

An open, transtrigonal, catheterless ureteral reimplant was performed with removal of the Deflux on both sides.¹² The subsequent histology of the resected Deflux showed both the granulomatous response to the dextranomer microspheres and the dextranomer microspheres themselves (Figure 2A). Giant cells are shown in Figure 2B, calcification is shown in Figure 2C, and the carrier substance (hyaluronic acid) is shown in Figure 2D.

During the four-year follow-up, the girl was infection-free and continent, with some improvement in right renal function on a dimercaptosuccinic acid (DMSA) scan to 30% overall function.

Case 2

Case 2 is a 4.5-year-old girl who presented with recurrent urine infections and bladder instability. Her cystogram showed bilateral, grade 5 VUR. A cystoscopy was performed, showing bilateral, golf-hole ureteral orifices, around which 0.3 ml Deflux paste was injected on each side, although no other detail was recorded for the procedure. The patient had continuous recurrent infections that led the parents to seek a second opinion. A MAG3 study identified



Figure 3: Ultrasound at referral for management after the Deflux injection showed the presence of a mound on the left side of the bladder, with no evidence of the Deflux paste on the right side.

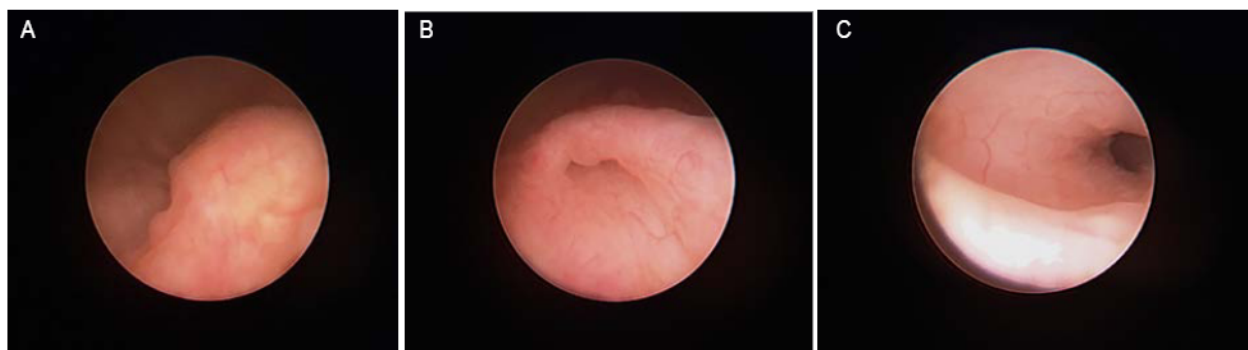


Figure 4: A – the mound of paste inferomedial to the left ureter orifice, which remained wide; the paste was not immediately adjacent, B – the right, wide ureteral orifice had no evidence of previous Deflux injection in the region, C – the inside of the right ureter, which could be entered with the cystoscope

persistent VUR and loss of function of both kidneys. Ultrasound could only identify the mound of Deflux paste on the left (Figure 3).

Follow-up cystoscopy revealed marked inflammatory changes in the bladder, causing deferral of planned open ureteral reimplants. In addition to the inflammatory changes, a mound of Deflux paste was seen inferomedially to the left ureteral orifice. The orifice was wide, with the paste not immediately adjacent to the ureteral opening (Figure 4A). The right ureteral orifice was wide and had no evidence of the previous Deflux injection in the region (Figure 4B), and could be entered during cystoscopy (Figure 4C).

Like case 1, an open, transtrigonal, catheterless ureteral reimplant was subsequently performed. Deflux was removed on the left side, but none was found on the right. The patient had a good recovery, and her bladder instability was managed. She had no further decline in her renal status or urine infections. Histology was not performed in this case.

Case 3

A 15-year-old girl had a minor congenital anorectal anomaly, which was investigated with a cystogram and cystoscopy soon after birth; however, both were recorded as normal. As an infant, she had recurrent urine infections investigated with ultrasound and a MAG3 study, which did not show VUR and identified functional, normal kidneys. On cystoscopy at the age of 3.5 years, the right ureteral orifice was recorded as open, and the treating surgeon injected 0.3 ml of Deflux paste into the region of each ureteral orifice. Notably, a precise description of the procedure was not given, though the ureteral orifice description differed from the findings recorded soon after birth.

The patient continued to experience irritative bladder symptoms, which were investigated with an ultrasound that showed calcific lesions on either side of the bladder base, and confirmed on a computed tomography scan. She was referred for a urological opinion

(Figure 5). Cystoscopy showed the mounds were mainly cranial to the ureteral orifices, and the bladder base showed trigonitis (Figure 6), which was the possible cause of her bladder irritation resulting in symptoms of needing to “push more out” at the end of voiding.

Discussion

First used in 1981, endoscopic VUR management has involved several substances.¹ Teflon, silicone, and dextranomer microspheres are three of the many substances considered and used. The first two are plastic particulate injections, with significant differences from Deflux; the latter consists of dextranomer microspheres in a hyaluronic acid carrier.² Teflon and silicone were largely abandoned in paediatric VUR management, due to concerns about migration and the inflammatory response to the plastic particles.³⁻⁵

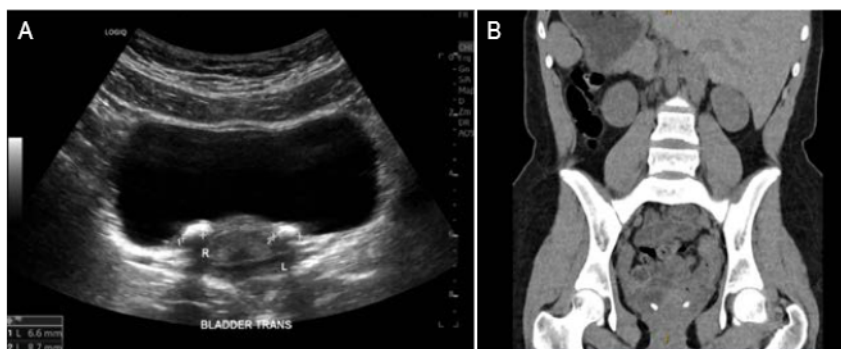


Figure 5: A – renal ultrasound identified bilateral bladder base calcification before urological referral for irritative bladder symptoms, B – consequent computed tomography scan showing the same bilateral bladder base calcification

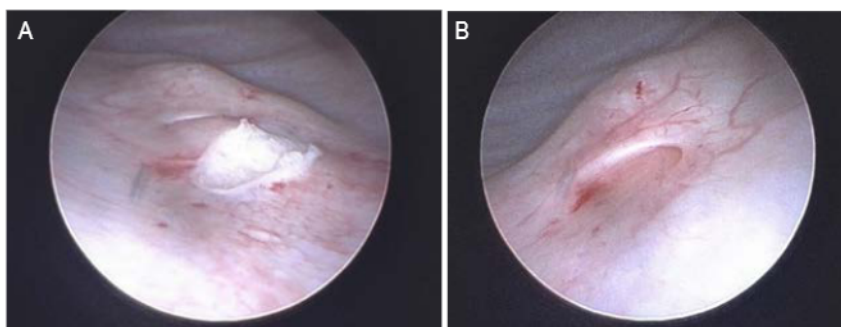


Figure 6: A – the slit-like orifice is seen with a large mound cranial to the orifice, and a smaller mound medially; the diffuse swelling in the trigone adjacent to the right ureteral orifice was incised to check if the Deflux mound might spontaneously extrude, which it did not, B – horseshoe orifice with the mound of Deflux paste cranially, without any obvious impact on the ureteral orifice configuration.

Deflux, the brand name for the dextranomer microspheres particle product, has been widely used; however, it is also associated with a chronic inflammatory response that seems underappreciated.^{1,13} The benefits of endoscopic VUR treatment include the procedure's minimally invasive nature and the high success rate for low-grade VUR. Nonetheless, there are problems with the need for reinjection, relatively poor results with high-grade VUR, extrusion of the paste, incorrect placement of the Deflux, and calcification and obstruction of the ureteral orifice.⁶⁻¹¹

Injected Deflux should be visualised on ultrasound, as the Deflux may disperse or extrude. Case 2 indicates that the carrier substance may persist for much longer than is currently recognised.¹⁴ Case 3 illustrates the long-term risk of calcification and confusion for those unfamiliar with the Deflux technique (note that case 1 showed microscopic calcification). Importantly, these findings suggest that the risks of dextranomer microspheres may be similar to those of plastics, as research on implant responses indicates that exposure duration and the inflammatory process may be the risk factors, although toxins associated with plastics may also contribute.³⁻⁵

Studies with histology and ultrasound follow-up are limited in the literature. Chertin et al.¹³ operated on 16 children with persistent reflux after Deflux injection, but did not provide any histological data nor comment on the appearance of the bladder at the injection site. The Great Ormond Street Hospital team identified three cases of calcification on ultrasound, prompting a review of all children treated with Deflux for VUR between December 2000 and January 2011. Two of the 104 children followed for four years or more (the lag time for the development of ultrasound-identified calcification) had developed injection-site calcification.⁶

In an abstract, Finkelstein et al.⁷ reported that 10% had hyperechogenic foci, detected at a mean of 9.8 months post-operatively. One became symptomatic, presenting with flank pain 2.4 years after the procedure. Kuipers et al.⁹ reported on a girl with a similarly calcified lesion in the bladder base and obstruction presenting five years after Deflux injection, noting that, like our third patient, a Deflux calcific mound can be found incidentally, as previously reported.⁸

The patient in whom we found the carrier substance (hyaluronic acid) present after two years shows a feature warranting further study, as most work on the injection of cosmetic fillers seems to assume that the substance is absorbed without an inflammatory response.¹⁴ However, specific studies of the Deflux mounds in the bladder after a protracted period have not been conducted beyond two years post-injection, and, unlike our patient, hyaluronic acid was not mentioned by that group.¹⁵

Limitations

The conclusions of this study are limited by the small number of cases, the retrospective nature of the study, missing procedural information, and histology available only in two cases.

Conclusion

Deflux is now widely used in managing VUR in children and has been FDA-approved since 2001. Our findings of undetectable paste, calcification of the Deflux mound, and persistence of the hyaluronic acid should lead to further, longer follow-up studies of patients treated endoscopically.

Conflict of interest

The authors declare no conflict of interest.

Funding source

None.

Ethical approval

Ethical approval was waived because of the paper's nature as a case report. Ethical approval for publication of Australian case studies is not required, provided there is no patient identification.

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