CASE REPORT

Coexistent duplication of urethra and a refluxing ectopic ureter presenting as recurrent epididymo-orchitis in a child

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SUMMARY

Congenital anomalies of the kidney and urinary tract (CAKUTs) occur in 3–6 per 1000 live births, accounting for most cases of paediatric end-stage kidney disease.¹ However, the molecular basis of CAKUT and anomalies of the external genitalia is poorly understood. We, herein, describe a case with left recurrent epididymo-orchitis with a coexistent urethral duplication and an ectopic ureter with an ipsilateral non-functioning kidney, which is, to the best of our knowledge, the first reported case of its kind. This case may bring about a paradigm shift in our comprehension of the development of the two entities. Understanding the pathogenesis may help develop preventive and renal preservation strategies. The Sonic hedgehog gene and bone morphogenetic protein 4 play crucial roles in preventing anomalies of the ureters and the external genitalia. In this article, we look at possible molecular pathways that could explain the synchronicity of this rare entity.

BACKGROUND

This case is extremely rare and accentuates the need for more research in this field to help determine the cause of occurrence of such entities and also help in preventing undue morbidity. Our patient presented with a refluxing ectopic ureter with an ipsilateral non-functioning kidney. He was earlier treated

conservatively for recurrent epididymo orchitis. Early detection of this condition is paramount and may have perhaps prevented recurrent inflammation of the testis and the kidney. The chronic reflux had rendered the ipsilateral kidney non-functional by the time the condition was diagnosed. Hence, this rare case needs to be brought to the attention of surgeons dealing with such patients.

CASE PRESENTATION

The patient in question is a 2-year-old boy who came to us with complaints of pain and swelling in the left testis for 3 weeks with history of fever. He was initially treated with oral antibiotics on an outpatient basis suspecting simple epididymo orchitis, but the swelling persisted. He did not have any urinary symptoms. He had had recurrence of similar symptoms at his home town over the past 2 years for which he was given multiple courses of antibiotics following which it would subside for a while.

On examination, his left testis was hard in consistency with scrotal oedema, warmth and tenderness. He was also found to have glanular hypospadias. A second meatal opening could not be made out. A urine culture sent in the outpatient clinic had grown carbapenem-resistant organisms for which he was admitted and treated with a full course of intravenous colistin.

INVESTIGATIONS

His imaging revealed the following:

Ultrasound scrotum—there was a well-defined heterogeneous mass in the left testis measuring 23×13×10 mm which had significant internal vascularity and the left epididymis could not be visualised separately. This was reported to be a probable inflammatory mass.

Ultrasound abdomen—there was moderate right-sided hydro ureteronephrosis. The left kidney was shrunken.

Vesicocystourethrography (VCUG)—simultaneous opacification of the bladder and reflux extending into a mildly dilated tortuous blind ending ureter noted on the left side. The ureter appears to be inserting ectopically into the posterior urethra. There is also an extra opacification of what looks like a stream refluxing into the vas (figure 1).

Retrograde urethrogram—a single meatal opening was present which was cannulated and

Figure 1 Ectopic ureteric insertion into bladder neck with possible stream refluxing into vas

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when contrast was injected, showed opacification of a single anterior urethra. In the subsequent voiding phase, opacification of two separate urethra was seen (figure 2).

The diagram illustrates the developmental pathways of the ureteric bud and urethra, focusing on the roles of Shh and BMP-4. It shows two main outcomes: ectopic ureter and urethral duplication, both resulting from a deficiency or defect of BMP-4.

Left Pathway (Normal Development):

- Shh** (blue box) leads to **UPREGULATION** of **BMP-4** (blue oval).
- BMP-4** **INHIBITS** **GDNF SIGNALING** (blue box).
- GDNF SIGNALING** **INHIBITS** **URETERIC BUDDING** (blue box).
- URETERIC BUDDING** leads to **ECTOPIC URETER.** (light blue box).

Right Pathway (Defect Scenario):

- BMP-4** (from the left) leads to the formation of the **URETHRAL PLATE** (blue oval), which contains **BMP-4** and **MSHGHG11E**.
- The **URETHRAL PLATE** leads to **URETHRAL PLATE Shh Expression** (blue oval).
- URETHRAL PLATE Shh Expression** leads to **URETHRAL PLATE** (blue oval), which contains **BMP-4** and **URETHRAL PLATE**.
- A **DEFICIENCY OR DEFECT OF BMP-4** (black box) leads to **URETHRAL DUPLICATION** (light blue box).

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graph TD
    Shh[Shh] -- UPREGULATION --> BMP4([BMP-4])
    BMP4 -- INHIBITS --> GDNF[GDNF SIGNALING]
    GDNF -- INHIBITS --> UretericBudding[URETERIC BUDDING]
    UretericBudding --> EctopicUreter[ECTOPIC URETER.]
    BMP4 --> UrethralPlate1([URETHRAL PLATE  
MSHGHG11E  
BMP-4])
    UrethralPlate1 --> UrethralPlate2([URETHRAL PLATE  
Shh Expression])
    UrethralPlate2 --> UrethralPlate3([URETHRAL PLATE  
BMP-4  
URETHRAL PLATE  
BMP-4])
    Defect[DEFICIENCY OR DEFECT OF BMP-4] --> UrethralDuplication[URETHRAL DUPLICATION]
```

TREATMENT

OUTCOME AND FOLLOW-UP

DISCUSSION

Targeted deletion of the sonic hedgehog gene (Shh) will result in a decrease or absence of the BMP-4 response thus increasing the susceptibility of developing ureterovesical junction abnormalities.^{3,4} Studies in mice have shown that the homozygous BMP-4 knockout mice is incompatible with life, whereas the heterozygous variety will have abnormalities reminiscent of the Congenital anomalies of the kidney and urinary tract (CAKUT) in humans.^{4,5} Another ureteric bud-inducing molecule which acts via the receptor, tyrosine kinase is the GDNF which may be responsible for the location of the ureteric buds.⁶ In vitro studies have demonstrated that BMP-4, has indeed inhibitory properties on this molecule (GDNF), thereby preventing ureteric ectopia.⁷

Bmp-4 is normally expressed in the mesenchyme that surrounds the urethral plate and the absence of Shh prevents the expression of this protein. Mice studies have shown that loss or abnormalities of this molecule along with a few others are responsible for altered urethral phenotypes.¹⁰ Pattens and Barrys hypothesis for urethral duplication attributes an abnormal association between the lateral folds of the genital tubercle and the ventral end of the cloacal membrane.¹¹

Learning points

- ▶ Recurrent epididymo orchitis should always trigger a suspicion for underlying urinary tract anomalies and warrants further investigation.
- ▶ Sonic hedgehog gene signalling defects and the non-expression of bone morphogenetic protein 4 may perhaps expound to a certain extent as to why coexistence of ectopic ureters and urethral duplication exists, but these are just deductive hypotheses based on in vitro experimentation and existing theories.
- ▶ Development of new strategies aimed at prevention of such anomalies and hence, preservation of renal function is the need of the hour.

Our patient had an ectopic ureter which was responsible for the vasal reflux causing recurrent epididymo orchitis and was also incidentally found to have a duplicate urethra. He was, however, found to have a non-functioning kidney by the time he came to us which highlights the need for early detection and better understanding of this phenomenon to assist in early detection.

He has had multiple episodes of testicular swelling at his home town which were dismissed as a 'run of the mill' epididymo-orchitis. This, perhaps has led to squandering of precious time wherein he could have been evaluated with a VCUG to demonstrate the vasal reflux, the vesicoureteric reflux and the concomitant existence of the duplicated urethra. This simple test would have put to rest any doubts as to the cause of his recurrent episodes of his epididymo-orchitis. With existing technology, further characterisation can be achieved with a CT abdomen or an MRI, intravenous urography and finally a cystourethroscopy.

Hence, it may be safely concluded that inactivation of Shh and the absence of Bmp-4 is the common thread that may help explain the coexistence of CAKUT and urethral anomalies. A flowchart has been created to highlight the possible role of Bmp-4 and Shh in the pathogenesis of this condition (figure 3).

The coexistence of ectopic ureters and urethral duplication is an extremely rare phenomenon and molecular mechanisms involved in the embryology of each, remains inadequately understood and much research in these fields remains to be seen.

Perhaps further molecular characterisation is necessary to discover the exact cause of this phenomenon which may lead to early recognition and prevention of renal failure in such patients.

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