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Bilateral Renal Hypoplasia with High β2-Microglobulinuria in the Neonatal Period

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Urinary β2 microglobulin (β2-MG) is a low-molecular-weight protein that is filtered by the glomerular basement membrane and absorbed by the proximal tubule epithelial cells. In perinatal management, urinary β2-MG levels are used to assess intrauterine inflammation in newborns, since urinary excretion increases during inflammation. Furthermore, β2-MG levels in fetal blood and urine are also used for predicting fetal renal function because β2-MG is not transferred to the placenta. Herein, we reported a patient with persistent high urinary β2-MG levels since neonatal period, who was later diagnosed with bilateral renal hypoplasia. If a newborn presents persistent hyper β2-microglobulinuria even without hematuria or proteinuria, congenital renal malformations should be considered.

INTRODUCTION

β2-microglobulin (β_2-MG) is a low-molecular-weight protein that is filtered through the glomerular basement membrane and absorbed by the proximal tubular epithelial cells [1]. For neonates including preterm infants, β_2-MG is regarded as an inflammatory marker since its excretion increases under inflammatory conditions such as chorioamnionitis [2]. Renal hypoplasia is the most common cause of chronic kidney disease in Japanese children [3]. The diagnosis of renal hypoplasia is generally based on the ultrasonographic findings of small-sized kidneys; however, an accurate diagnosis of renal hypoplasia during the neonatal period can be difficult as no reliable reference range for renal size is available. Also, since patients with renal hypoplasia rarely show hematuria or proteinuria during the neonatal period, screening and identification by normal urinalysis is difficult. Here, we report a case of bilateral renal hypoplasia diagnosed in a child at 5 years of age, who presented with persistent high β_2-microglobulinuria since his neonatal period without any evident abnormality in renal imaging.

CLINICAL CASE

A male infant, the first offspring of a dichorionic diamniotic twin born at 37 weeks 5 days of gestation, with a birthweight of 2735 g, was transferred to our hospital on day 7 after birth due to poor feeding and body weight loss. His perinatal and family history was normal.

The mother was a primipara, and her pregnancy course was not complicated with infections or abnormal ultrasonography findings; however, she required tocolytic due to threatened preterm labor. The infant was born without asphyxia (Apgar scores of 9 at 1 min and 10 at 5 min) by cesarean section. The prenatal cardiotocography showed a normal waveform.

The clinical and laboratory examination revealed dehydration accompanied by electrolyte disorders. Ultrasonography revealed bilateral normal-sized kidneys (right and left kidneys, 3.2 and 3.6 cm in diameter, respectively) with grade II left hydronephrosis (**Fig. 1**).

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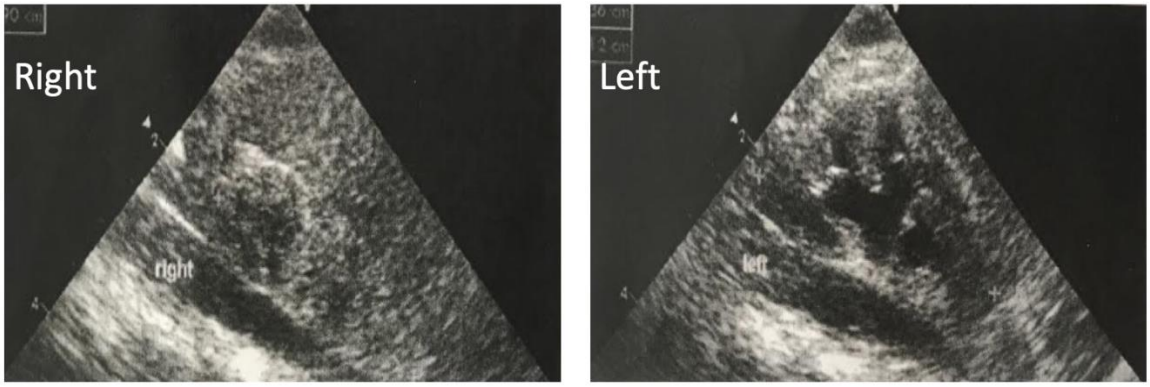

Figure 1. Renal ultrasound images on 7-day after birth.
Ultrasonography revealed bilateral normal-sized kidneys (right kidney diameter, 3.2 cm; left kidney diameter, 3.6 cm) with grade II left hydronephrosis.

The urinalysis showed no other abnormalities but revealed an extremely high β_2-MG/creatinine (Cr) ratio (205 μg/mgCr) relative to the normal range of 24–78 μg/mgCr [4]. The patient recovered after intravenous fluid therapy and was discharged on day 30 with oral sodium chloride supplementation. However, his urinary β_2-MG excretion did not decrease throughout the follow-up period, even though the serum CRP levels (inflammatory marker) consistently remained <0.1 (**Fig. 2**).

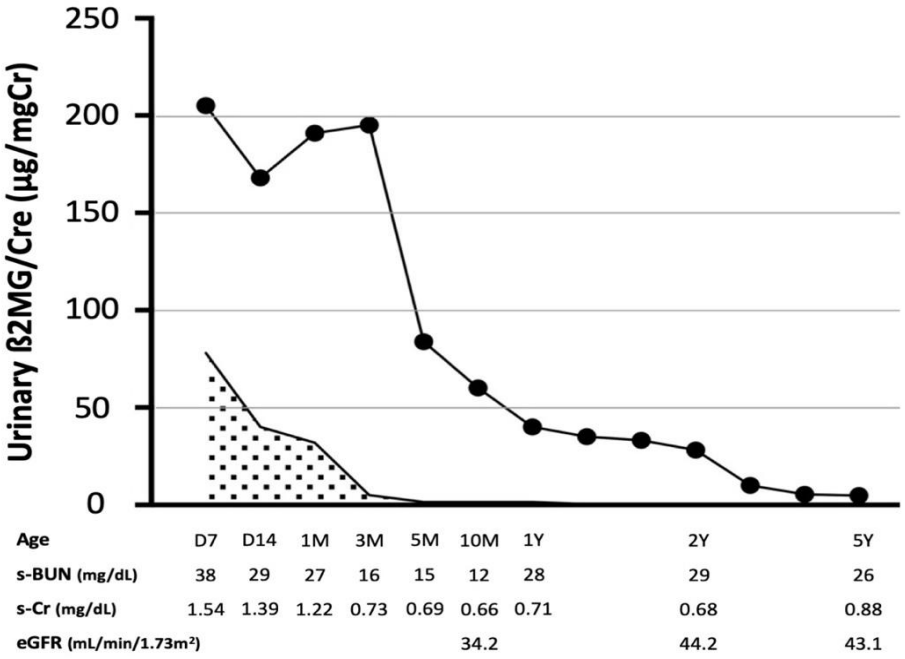

Figure 2. The changes in urinary β2-microglobulin (β_2-MG) levels.
u-Cr, urinary creatinine; u-RBC, urinary red blood cells; u-protein, urinary protein.
The urinary β_2-MG/Cr ratio of the patient (●, solid line) was 2 standard deviations above that of normal neonates and children (dotted area, referenced from *Kidney Int.* 1983; 24: 358-363 [5] and *Pediatr Int*. 2015; 57: 79-84 [6]).

Therefore, a detailed renal examination was performed, which included ultrasonography (1 year and 9 months, renal atrophy in the right kidney, **Fig. 3**), Tc-99m DMSA images (2 years, reduced renal function in both kidneys, **Fig. 4**), magnetic resonance imaging (2 years, no urinary tract anomaly), and renal biopsy of the left kidney (5 years, oligomeganephronia, **Fig. 5**). Based on these results, we diagnosed him with bilateral renal hypoplasia.

At 10 years of age, targeted sequencing using next-generation sequencing was conducted for 172 genes that are associated with congenital anomalies of the kidney and urinary tract (CAKUT); however, no causative

mutations were identified. Written informed consent was obtained from the patient for publication of this case report and accompanying images.

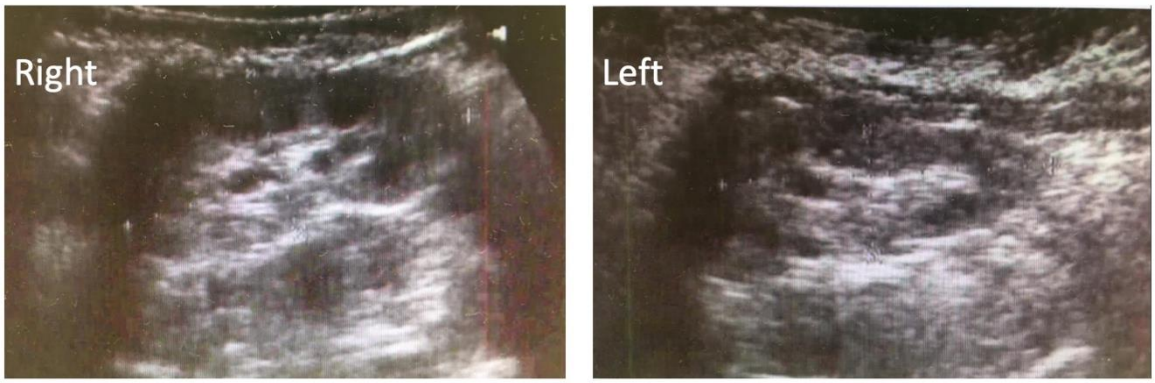

Figure 3. Renal ultrasound images at 1 year and 9 months.
Ultrasonography revealed renal atrophy in the right kidney and a normal-sized left kidney (right kidney diameter, 4.2 cm [normal range, 5.5–6.6 cm] [7]; left kidney diameter, 6.0 cm [normal range, 5.4–7.2] [7]), respectively).

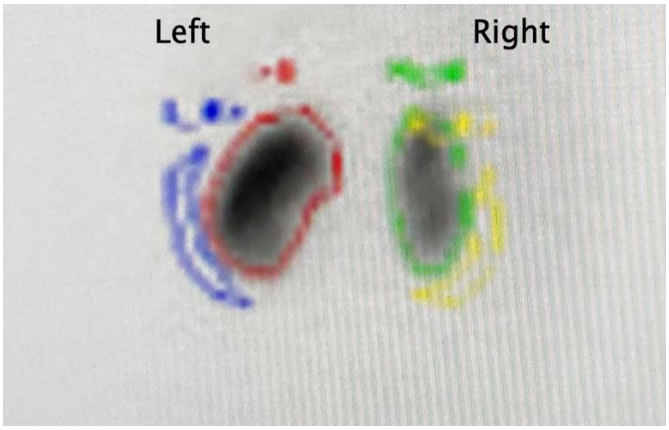

Figure 4. Tc-99m DMSA images at 2 years.
Tc-99m DMSA revealed reduced renal function represented as reduced renal intake rate of both kidneys (Rt kidney; 10.9% and Lt kidney; 26.1%, respectively (normal range; 45-55% [8])).

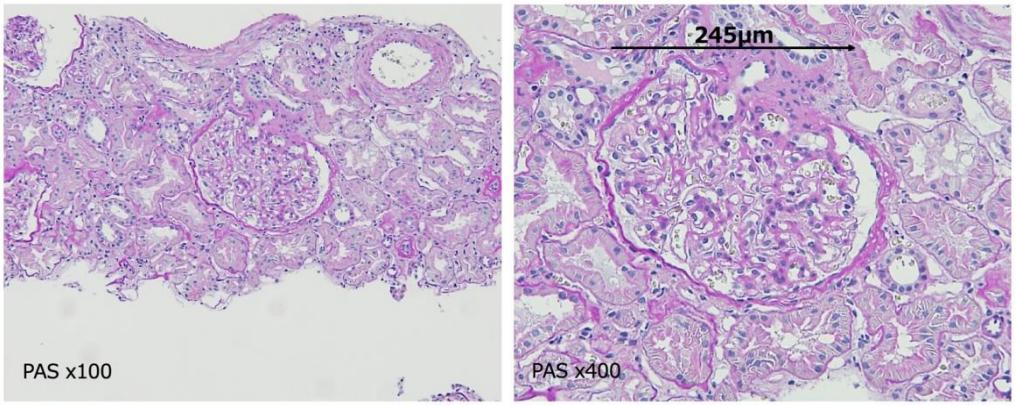

Figure 5. Renal histology of the left kidney at 5 years.
The number of glomeruli in one slice was low (Left; Periodic acid–Schiff, 100×). The glomerular diameter was 245 μm in this case, which was larger than the average size of normal glomeruli (200 ± 28 μm) [9].

DISCUSSION

The present case showed extremely high β_2-microglobulinuria during his neonatal period. High β_2-microglobulinuria is usually observed due to increased serum β_2-MG secretion and urinary excretion caused by inflammation or reduced reabsorption of β_2-MG in the proximal tubules of patients with CAKUT.

In neonates, urinary β_2-MG levels are generally high (24–78 μg/mgCr), which may reflect the renal immaturity [5]. In particular, preterm infants exposed to fetal distress showed higher urinary β_2-MG levels than did term infants [1]. Nishimaki et al. reported that urinary β_2-MG levels in very preterm infants were high (45–187 μg/mgCr) in comparison with term infants, and decreased spontaneously at 1 month (15–130 μg/mgCr) [2]. Intriguingly, the urinary β_2-MG levels were significantly higher in preterm infants of 23–28 weeks' gestation with histological chorioamnionitis compared to those without histological chorioamnionitis [2]. They also reported increased urinary β_2-MG levels in premature infants soon after birth who subsequently developed chronic lung disease, and suggested this elevation might reflect the conditions of fetal inflammatory response syndrome [10].

Fetal serum β_2-MG levels are also used to predict the prognosis of fetal renal function and are significantly increased in fetal patients with CAKUT and with poor renal prognosis. Based on fetal urine sampling data at < 23 weeks of gestation, Abdennadher et al. reported that fetal urinary β_2-MG levels correlated with renal function in fetal patients with CAKUT [4]. In our case, urinary β_2-MG on admission was extremely high (205 μg/mgCr), even higher than the upper range of urinary β_2-MG in very preterm infants [2], and the elevated β_2-MG levels persisted even after 1 month of age.

In conclusion, a detailed follow-up is required for newborns with extremely high β_2-microglobulinuria to rule out congenital renal diseases.

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