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JCIMCR OPEN ACCESS Journal of Clinical Images and Medical Case Reports

ISSN 2766-7820

Case Report

Open Access, Volume 3

Mutation in TBX18 and renal abnormalities: A case report and review of literature. Point of view of Nephrologist

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Received: May 16, 2022

Accepted: Jun 14, 2022

Published: Jun 21, 2022

Archived: www.jcimcr.org

DOI: www.doi.org/10.52768/2766-7820/1903

Abstract

Mutation in TBX18 is rare. It was linked to some various phenotypes mainly congenital anomalies of the kidneys and urinary tract but never renal angiomyolipoma.

Here we report the first association of renal angiomyolipoma and mutation in TBX18 and we detailed genetic analyses of renal angiomyolipomas as well as consequences of mutation in TBX18 in humans.

Introduction

Mutation in TBX18 is rare. The gene belongs to the T-box gene family, a large group of transcription factors involved in many aspects of embryonic development [1]. Mutation in TBX18 is rare. Dominant-negative TBX18 mutations cause human anomalies in the kidney and urinary tract by interference with TBX18 transcriptional repression, thus implicating ureter smooth muscle cell development in the embryological period [2-5]. The congenital anomalies of the kidney and urinary tract are likely ureteropelvic junction obstruction but also hypo/dysplasia [2-7]. Renal angiomyolipoma has never been reported.

Here we report the first association of renal angiomyolipoma and mutation in TBX12 and we detailed genetic analyses of renal angiomyolipomas as well as consequences of mutation in TBX18 in humans.

Case report

We report the case of a 36 -years-old woman referred to our nephrology clinic for renal workup as she was diagnosed with TXMB19 mutation. The patient has a gynecology history of 4 gravidities, 3 parities and 2 intrauterine fetal demises intrauterine fetal demises. The first intrauterine fetal demise was in 2015. Diagnosis of severe congenital malformations was early done by an ultrasound of second trimester done at 14 weeks and 5 days gestation, which found a prominent fluid filled areas measuring approximately 5 mm in diameter in either side in the region of fetal kidneys due likely to prominent renal pelvis in either side. Kidneys were not clearly delineated. After complete investigation, the fetus was found to have severcongenital malformations with sever left sided congenital diaphragmatic hernia, with the bowel, stomach and a part of the liver in the left side of the chest. The heart was compressed at the right with congenital defects and bilateral hydronephrosis with no evidence of posterior urethral valves. The urinary bladder was normal, and theamniotic fluid index was good. The glucose tolerance test was normal. The fetus Karyotype and chromosomal microarray analysis were normal. The vital prognosis of the fetus was poor due mainly to the sever lung hypoplasia, even with a corrective surgery for the hernia with high likely of intrauterine fetal demise.

The patient at 27 weeks gestation was reviewed with all the above findings. She opted for no monitoring, no lower segment cesarean section for fetal reasons and no attempt of neonatal resuscitations. The plan was to wait till the patient start normal labor pain, operative intervention was preserved for the maternal indications only.

At 39 weeks gestation, the patient delivered normally by vaginal delivery.

The second pregnancy in 2018 was dichorionic diamniotic pregnancy with growth discrepancy conceived by in vitro fertilization. She developed gestational diabetes on diet and albuminuria at 3+ with normal renal function. She was diagnosed at 27 weeks 5 days gestation by ultrasound to have one twin with congenital anomalies with renal right pelvic dilatation, biometry parameters at 5%, estimated fetal weight less than 5% and right renal pelvic dilatation of 7 mm. She delivered at 36 weeks of gestation bycesare an section, one healthy daughter, and the other twin was intrauterine fetal demise diagnosed at 35-week gestation and died 6 hours after delivery.

The pathology of placenta showed fused twin placentas with attached fetal membranes and umbilical cords. There are no anastomosis present. The placentas are joined by an opaque common membrane. The fetal membranes are thickened and hemorrhagic and inserted marginally. The fetal surface is. The fetal membranes are tinged green and inserted marginally. The first fetal surface is focally hemorrhagic and the second tinged green. The cord has 2 false knots measuring 1.8 and 2 cm in greatest dimension. The maternal surface is hemorrhagic and focally disrupted. Placental parenchymal cut surfaces are hemorrhagic with a yellow lesion measuring 1 cm in greatest dimension.

The XR Skeletal survey of the dead newborn showed collapsed skull bones with soft tissue (Figure 1).

The genetic segregation test of the 2 first healthy kids was heterozygous for likely pathogenic variantTBX18 gene and heterozygous for variant of uncertain significance for FBXL4 gene.

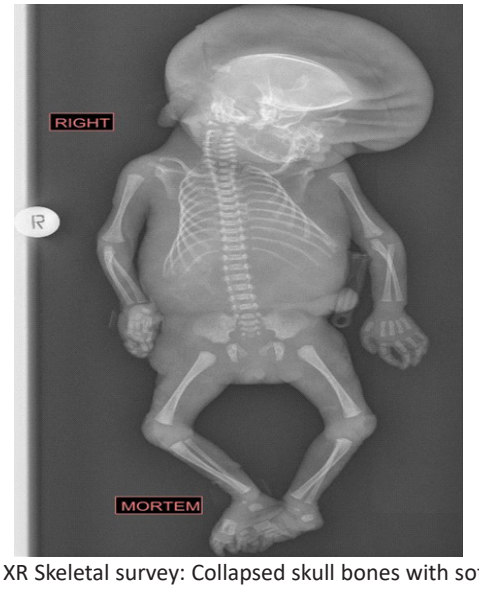

Figure 1: XR Skeletal survey: Collapsed skull bones with soft tissue swelling. Triangular thoracic cage.

The Patient found to have also pathogenic variant in TBX18 gene and referred to both nephrology and urology clinic.

Upon presentation in our nephrology clinic, blood pressure was 129/80, temperature 36.4, heart rate 98, Her physical examination was unremarkable with non-tender, non-distended abdomen and no lower limb edema. Laboratory results revealed normal renal function with serum creatinine level at 49 umol/l, eGFR>60, urea at 3.8 mmol/l, sodium at 137 mmol/l, potassium at 3.9 mmol/l, chloride at 97 mmol/l, bicarbonate at 25 mmol/l, White blood cells at 8600, hemoglobin at 10.1 g/dl , corrected calcium at 2.28 mmol/l and urine protein ratio=30.68 mg/mmol. The ultrasound abdomen and pelvis revealed normal sized right and left kidneys of 12.6 x 4.7 cm and 12.2 x 4.3 cm respectively with normal cortical echogenicity and Left kidney measures about. Presence of a small hypoechoic structure in the left kidney lower pole measures about 4 mm likely represent angiomyolipoma (Figure 2).

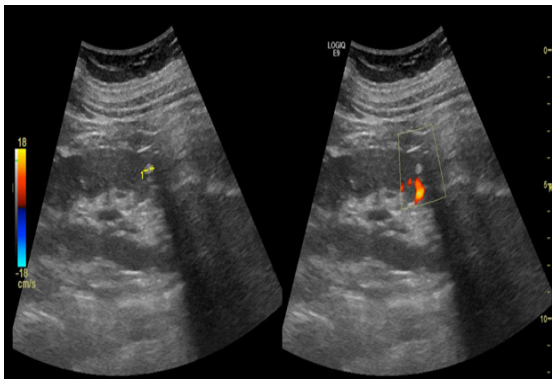

Figure 2: Left kidney with small angiomyolipoma.

Discussion

There are several learning points that can be made in this case with review of literature as we report the first case of mutation in TBX18 in a young women associated to renal angiomyolipoma.

Renal angiomyolipoma is the most common benign kidney tumor and represents 1-3% of solid renal tumors. It is a mesenchymal tumor characterized by an abnormal thick-walled blood vessels, smooth muscles and fat and is a part of the spectrum of perivascular epithelioid cell neoplasms.

There are three types of renal angiomyolipomas including the angiomyolipoma, the Epithelioid angiomyolipoma which is a rare variant of renal angiomyolipoma with malignant potential, and Tuberous Sclerosis Complex -related renal angiomyolipoma which is genetic disease Tuberous Sclerosis Complex, defined as an autosomal dominant disorder characterized by multiple benign tumors throughout the body, including the brain, skin, lungs and kidneys [8].

Renal angiomyolipoma observed in Epithelioid angiomyolipoma are likely large with presence of tumor necrosis and venous invasion with high risk of malignant transformation, recurrence, metastasis and fatal outcome [9,10].

Renal angiomyolipoma observed in Tuberous Sclerosis Complex have incidence of 70% and are likely large, multiple and bilateral [11-14].

Most renal angiomyolipomas are sporadic and asymptomatic if the tumor size is small, observed mainly in normal individuals, non-Tuberous Sclerosis Complex with an incidence of 0.1% and they are likely small, unique, and unilateral in location as in our case [15,16].

Renal angiomyolipomas are often identified as an incidental finding on abdominal imaging studies done for other reasons. In our case, it was discovered on abdominal ultrasound done to rule out congenital anomalies of the kidneys and urinary tract as the patient has mutation in TBX18.

In general, they are clinically insignificant in normal individuals, non-Tuberous Sclerosis Complex as our case. Their chief clinical significance is that large lesions are prone to spontaneous hemorrhage, progressive lesions can compromise renal function, and fat-poor angiomyolipoma are difficult to distinguish from other renal neoplasms [16].

Although genetic is well established in Tuberous Sclerosis Complex with germline mutation on chromosome arm 16p leading to bi-allelic inactivation of the Tuberous Sclerosis Complex 2, and much less commonly Tuberous Sclerosis Complex 1 [17-21], it is uncertain and poor studied is sporadic angiomyolipomas. It was reported mainly the same mechanism with a loss of heterozygosity or inactivating mutations of the Tuberous Sclerosis Complex 2 gene leading to a reduction in its suppressive expression [1,6,22-24] and therefore to mTORC1 activation [23-27] but also a P53 gene mutation located on the short arm of human chromosome 17 and coding for the phosphoprotein p53 [28]. It was advanced a neural crest origin related to melanocyte development [29,30].

No evidence for other genetic alterations has been found [31].

However, in our case report, a mutation in T-Box Transcription Factor 18 (TXB18) was found, never been described previously in association with renal angiomyolipoma. Is there a significant relation or is it a hazardous coincidence?

We will try along our discussion to review the possible consequences of such mutations especially on the urinary tract.

TBX18 belongs to the T-box gene family, a large group of transcription factors involved in many aspects of embryonic development [1].

TBX18 gene is located on arm q of the chromosome 6, in the Regions 14.3 close to the centromere. It has 8 exons, coding for an encoded protein which belongs to the vertebrate specific Tbx1 sub-family. The TBX18 transcription factor regulates patterning and differentiation programs in the primordia of many organs [2]. TBX18 is essential for developmental specification of the ureteric mesenchyme and ureteric smooth muscle cells [5].

Mutation in TBX18 is rare. Dominant-negative TBX18 mutations cause human anomalies in the kidney and urinary tract by interference with TBX18 transcriptional repression, thus implicating ureter smooth muscle cell development in the embryological period [2-5]. The congenital anomalies of the kidney and urinary tract are likely ureteropelvic junction obstruction due to the chronic inflammation and long-term micro-trauma created by the disease in the embryological period [2,4,5]. Congenital Anomalies of the Kidneys and Urinary Tract can include also renal hypo/dysplasia, occurring by loss of essential TBX18 function during nephrogenesis or in the condition of lack of urine transport in a maldeveloped ureter and the resultant intrarenal pressure which interferes with proper renal development [6,7].

In mice, Tbx18 has been shown to be selectively expressed in ureteral mesenchyme and to regulate ureteral smooth muscle differentiation [22]. Mouse models lacking Tbx18 show malformed ureters resulting in various types of obstructive uropathy phenotypes as well as kidney parenchymal damage. The latter was suggested to be secondary to urine outflow obstruction, but TBX18 might also play a role during kidney development with various and heterogeneousurinary tract phenotypes with predominant obstructive uropathy [7,22].

Our patient doesn't have anomalies in the kidney and urinary tract but a small angiomyolipoma in the left kidney.

Congenital anomalies of the kidneys and urinary trac are the most common cause of chronic kidney disease in the first three decades of life [5].

Our patient renal function is normal.

The TBX18 transcription factor regulates patterning and differentiation programs of many organs, other than kidneys [2].

TBX18 was suggested to regulate the normal development of the sinoatrial node [32,33]. Mutation in TBX18 was previously related to heart disease likely conduction abnormalities as sick sinus syndrome or atrioventricular block [34].

Biological pacemakers that combine cell-based and gene-based therapies with overexpression of Tbx18 are a promising treatment for these cardiovascular diseases and prevention and reversion of pacemaker-induced cardiomyopathy by restoring antegrade conduction [35-38]. It is controversial in some studies [39]. Consequently, Tbx18 gene therapy was recently used for biological pacing in porcine model of heart block [40].

Atherosclerosis is a widespread and complicated disease involving phenotypic modulation and transdifferentiation of vascular smooth muscle cells, the predominant cells in aorta, as well as changes in endothelial cells and infiltrating monocytes. TBX18 has been reported as playing a role on atherosclerosis as atherosclerosis-and contractile vascular smooth muscle cells -related genes by exhibiting hypermethylated differentially methylated regions at aorta enhancer chromatin as well as known genes ACTA2 (Aorta A2 Smooth Muscle Actin), ELN (Elastin), MYOCD (Myocardin), C9orf3 (Mir-23b And Mir-27b Host Gene), and MYH11 (Smooth Muscle Myosin) [41].

Rare cases of Langerhans cell histiocytosis, which is characterized by multisystem organ involvement and poor prognosis of the colon lesions with genetic mutations including TBX18 mutations on genetic testing werereported [42].

On the other hand, Tbx18-null mice die shortly after birth due to severe malformations of the axial skeleton [43].

Our patient doesn't present a phenotype of TBX18 mutations. In fact, phenotypes depend on dominant or recessive TBX18 mutations. The phenotypes of the mices with dominant TBX18 mutations were milder compared to recessive Tbx18 mutations in null mice phenotype. Nonetheless, the dominant human phenotype was more severe when compared to the phenotype of the heterozygous mice. This apparent discrepancy might again be explained by a dominant-negative effect in which specific heterozygous mutations cause more severe effects than simple heterozygous null alleles of the same gene.

Conclusion

Mutation in TBX18 is rare. It was linked to some various phenotypes mainly congenital anomalies of the kidneys and urinary Tract but never to renal angiomyolipoma. We reported the first association of renal angiomyolipoma and mutation in TBX18 and we don't know if a significant relation is there or is it a hazardous coincidence as the consecutive genes are located in different chromosomes. More genetic studies should be performed to elucidate phenotypes of mutations in TBX18.

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