

# Bladder paraganglioma with renal agenesis: A possible new association and its implications in the light of REarranged in transfection gene genetics

Rohan Satish Valsangkar, Niraj K. Goyal, Shailesh P. Bajania, Syed J. Rizvi

Department of Urology and Transplantation, Institute of Kidney Diseases and Research Centre and Institute of Organ Transplantation, Ahmedabad, Gujarat, India

## Abstract

Pheochromocytoma/paraganglioma and renal agenesis are commonly reported conditions. Their coexistence, however, is rare, with few cases reported. We report the case of a 21-year-old male who presented with painless hematuria. He was found to have congenitally absent right kidney along with bladder mass on imaging. Examination including blood pressure was normal. He underwent cystoscopy that showed a solid looking tumor on the anterior wall. Paraganglioma was suspected due to intraoperative rise in blood pressure during resection and was confirmed on histopathology. Subsequently after work up and preoperative alpha blockade, patient underwent partial cystectomy and excision of the paravesical mass. Histopathology showed paraganglioma confined to bladder wall with surgical margins free and a paravesical mass that was seminal vesicle cyst. On follow-up, patient is normotensive and asymptomatic. This coexistence of paraganglioma and renal agenesis may have a common genetic mechanism in the form of REarranged in Transfection (RET) gene mutation. This is a well-characterized gene, mutations of which are known to be associated with both conditions. Current knowledge of the role of RET gene in both conditions is reviewed to put forth RET mutation as the possible common underlying genetic mechanism along with possible clinical implications of the combination.

**Key Words:** Bladder paraganglioma, pheochromocytoma, Rearranged in Transfection gene, renal agenesis

## Address for correspondence:

Dr. Rohan Satish Valsangkar, Department of Urology and Transplantation, Institute of Kidney Diseases and Research Centre and Institute of Organ Transplantation, Civil Hospital Campus, Asarwa, Ahmedabad - 380 016, Gujarat, India. E-mail: rsvalsangkar@gmail.com

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## INTRODUCTION

Paragangliomas and unilateral renal agenesis/hypoplasia are well-reported conditions. Their combination, however, is rare with few cases reported.<sup>[1-3]</sup> Bladder paraganglioma is rare among paragangliomas.<sup>[4]</sup> We report its association with renal

agenesis for the first time. REarranged in Transfection (RET) gene mutations are proven to cause both of these conditions. RET mutation as a possible common mechanism of the both conditions is discussed briefly along with literature review and possible clinical implications of the association.

## CASE REPORT

A 21-year-old male presented with hematuria for 6 months. He did not have any other symptom including weight loss/palpitation suggestive of paraganglioma. Physical examination including blood pressure was normal. Biochemical investigations showed normal hemogram and renal function. Urine analysis showed microhematuria and urine cytology was negative for

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malignant cells. Ultrasonography showed single anterior wall bladder mass of size 2.6 cm with absent right kidney. Patient underwent cystoscopy that showed a solid appearing tumor with overlying calcification on the anterior wall close to the bladder neck and left hemitrigone. Transurethral resection of the tumor was done. Intraoperatively patient developed high blood pressure (230/110 mm of Hg) that required nitroglycerine infusion for control. Histopathology was paraganglioma [Figures 1 and 2]. Subsequent computed tomography scan confirmed normal adrenals with right renal agenesis and right paravesical mass [Figure 3] apart from bladder mass [Figure 4]. Preoperative workup was done to rule out other synchronous paragangliomas. After optimization with alpha blockers, patient underwent partial cystectomy along with excision of paravesical mass. Histopathology showed paraganglioma being confined to anterior bladder wall with no extravesical spread [Figure 5] and surgical margins being free. The paravesical mass was seminal vesicle cyst. Postoperative recovery was uneventful and after 8 months, patient is voiding well and is normotensive.

## DISCUSSION

Bladder paragangliomas are rare (<0.05%) bladder tumors and account for <1% of all paragangliomas.<sup>[4]</sup> Hematuria, micturition attacks, and hypertension are seen in approximately 50% cases. They present at a mean size of 3.9 cm and partial cystectomy is done in 70% of cases in a recent review of 106 paragangliomas from 1980 to 2012.<sup>[4]</sup> Paragangliomas, in general, are proven to have underlying germline (inherited) mutations in 40% cases in 12 genes so far, one of the important gene being RET.<sup>[5]</sup> It also has a major role in renal development.<sup>[6]</sup>

With a mutated common gene, it is logical to expect association of congenital renal abnormalities and chromaffin tumors (those due to RET mutations). However, we noted only three cases of renal agenesis/hypoplasia associated with chromaffin tumors in literature.<sup>[1-3]</sup> To our best knowledge, we are reporting first extra-adrenal paraganglioma case associated with renal agenesis. The following discussion is an endeavor to explain

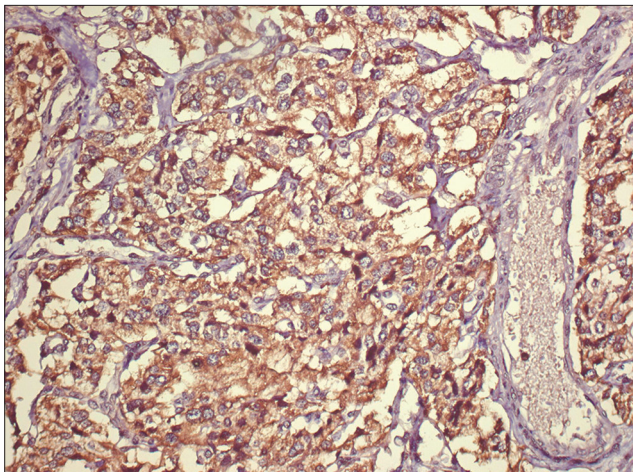


Figure 1: Immunohistochemistry chromogranin (x200)

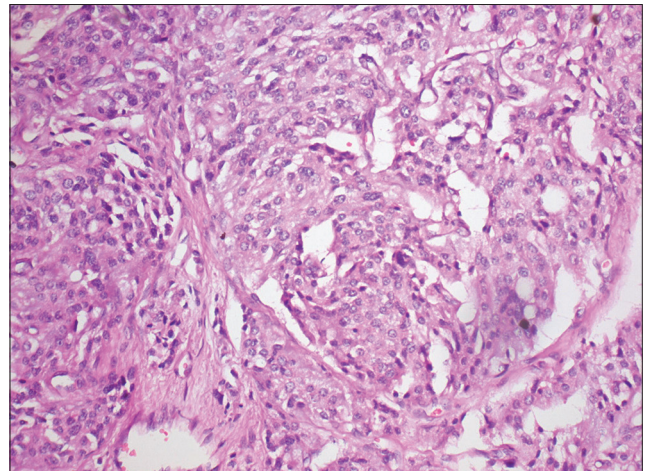


Figure 2: Paraganglioma (H and E, x200)

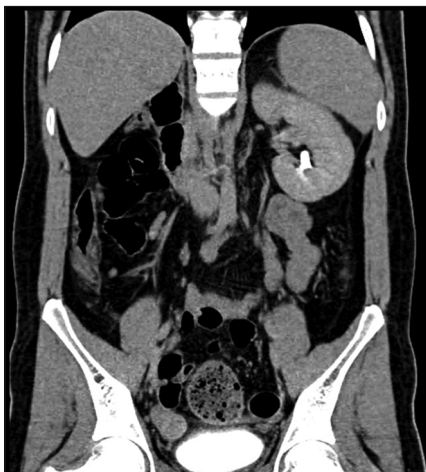
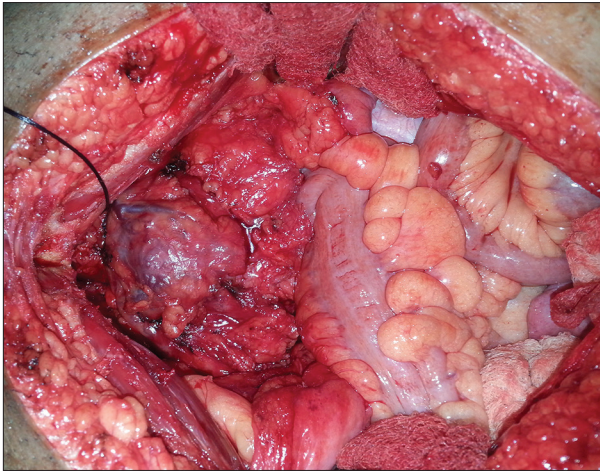


Figure 3: Paravesical mass that was dilated seminal vesicle cyst a well-known association with renal agenesis



Figure 4: Anterior bladder wall paraganglioma





**Figure 5:** Anterior bladder wall paraganglioma externally, stitch to control dorsal venous complex before proceeding to partial cystectomy

this association in the light of role of RET gene uncovered in embryology and cancer biology.

REarranged in Transfection gene is located on chromosome 10 and gene product is a cell membrane receptor of tyrosine kinase family. Ligand (molecule which attaches to receptor) of glial cell line-derived neurotrophic factor (GDNF) family binds to RET receptor resulting in activation of multiple downstream pathways that promote cellular proliferation, survival and/or differentiation. Gain of function mutations cause persistently activated receptor in the absence of ligand promoting malignant transformation. RET mutations are well-established cause of multiple endocrine neoplasia type 2 (MEN2) syndromes (medullary carcinoma thyroid, adrenal pheochromocytoma, ganglioneuromas).<sup>[5,6]</sup> Incidence of RET mutation in paraganglioma is variably reported but estimated to be 5% in a recent review article.<sup>[5]</sup>

In embryogenesis, GDNF to RET receptor interaction is critical for neural development, metanephric mesenchymal induction by ureteric bud and late renal morphogenesis.<sup>[6]</sup> Phenotypic spectrum that is seen due to loss RET mutation may be influenced by the effect of other genes on the RET pathway. For instance, loss of function mutation in RET gene causes defect in enteric nervous system (analogous to Hirschsprung disease), renal agenesis or congenital anomalies of urinary tract depending on combination of RET and Spry1 (another gene involved in renal development) in transgenic mice experimentally.<sup>[6]</sup> Clinically, evidence of RET mutation in renal agenesis is supported by a study of stillborn fetuses showing 20% RET mutation rate in unilateral renal agenesis.<sup>[7]</sup>

How can loss of function phenotype (renal agenesis) possibly coexist with a gain of function phenotype (pheochromocytoma)? Different RET mutations in different cases are described.<sup>[2,8]</sup>

A subset of RET mutation (called Janus mutation) may have a negative role in neural and/or renal development but promote cellular proliferation. Experimental evidence for such mutation was found when a particular type of RET mutation was found to promote cellular proliferation but which impaired GDNF action on RET on cellular migration and differentiation *in vitro*.<sup>[9]</sup> Clinical support for paradox is found in a MEN2A case with renal agenesis, one of the three cases of renal agenesis with pheochromocytoma described previously.<sup>[2]</sup> Further, same gene mutation may manifest with only loss of function phenotype in one generation but with loss and gain of function mutation in a different generation, for example, familial renal agenesis with medullary carcinoma thyroid in a mother and with Hirschsprung disease in son.<sup>[8]</sup> Similarly “carriers” of MEN2 patients having renal agenesis have been described, who possibly show only one manifestation of the full spectrum of RET mutation effects.<sup>[10]</sup> Precise molecular mechanisms in such cases remain to be elucidated completely.

However, we do realize potential problems in conjuncture of RET mutation being an underlying common link for renal agenesis and paraganglioma. It is well known that unilateral renal agenesis is a common condition (1 in 1000 live births) and so association with paraganglioma may be incidental. Also, reported RET mutation incidence in renal agenesis is variable, quoted as 7–20% in stillborn fetuses.<sup>[7,11]</sup> However, this may be explained as a common final pathway of RET gene being influenced by mutation in other modulating genes. It can also be due to low penetration of RET gene to cause renal agenesis as compared to high penetration for malignant transformation.<sup>[10]</sup> In our case, we could not carry out testing for RET gene due to financial constraints of the patient.

To summarize, this is the first reported case of extra-adrenal paraganglioma with renal agenesis to the best of our knowledge. Though the exact cause of association remains unproven in our case, RET mutation may be the common underlying mechanism. Clinically, if such a combination is found, it is worthwhile to elicit family history for congenital megacolon, renal anomalies, and to test for manifestations of MEN2 syndrome and RET gene. Different manifestations of same RET gene mutation in different individuals may be due to the influence of other genes on RET pathway and need further study.

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