Annals of Case Reports
Diamantidis D, et al. Ann Case Rep: 8: 1209
www.doi.org/10.29011/2574-7754.101209
www.gavinpublishers.com

OPEN ACCESS
GAVIN PUBLISHERS

Case Report

Hereditary Papillary Renal Carcinoma: A Case Report

Diamantidis D, Tsakaldimis G, Lailisidis S, Panagiotopoulos N, Kafalis C, Giannakopoulos S, Deligeorgiou E, Kouroupi M, Giatromanolaki A, Christos Kalaitzis*

Department of Urology, University of Thrace, 68100 Alexandroupolis, Greece

***Corresponding authors**: Christos Kalaitzis, Department of Urology, University of Thrace, 68100 Alexandroupolis, Greece

Citation: Diamantidis D, Tsakaldimis G, Lailisidis S, Panagiotopoulos N, Kafalis C, et al (2023) Hereditary Papillary Renal Carcinoma: A Case Report. Ann Case Report. 8: 1209. DOI:10.29011/2574-7754.101209

Received: 05 March 2023, **Accepted:** 09 March 2023, **Published:** 13 March 2023

Introduction

Renal cell carcinoma (RCC) accounts for 2-3% of adult malignancies, with an estimated 3% of cases linked to an inherited predisposition [1-3]. Hereditary papillary renal cell carcinoma (HPRCC) is a rare form of kidney cancer that is inherited in an autosomal dominant manner with incomplete penetrance [4]. HPRCC is caused by activating mutations in the MET proto-oncogene, which is located on chromosome 7q31-34 [5]. This type of cancer is characterized by the tendency to develop multiple tumours in both kidneys, known as multifocal and bilateral papillary renal cancers. However, the exact prevalence of HPRCC is not well established [6,7]. Individuals who have known or likely pathogenic mutations in the MET gene have an increased risk of developing multiple tumours in both kidneys, with a risk greater than 80%, while some studies have reported even higher rates of tumour development [1]. These tumours can be found as early as the patient's 20s, but are more commonly detected after the age of 50, with a median age of diagnosis being 57 years old [1,8]. Detecting HPRCC tumours in imaging studies may be challenging due to their hypo vascularity and may be mistaken for cysts [7]. Magnetic Resonance Imaging (MRI) or Computed Tomography (CT) is recommended for at-risk HPRCC family members, rather than ultrasound, with most institutions starting cross-sectional abdominal imaging every 1-2 years at the age of 30 in patients with a known family history [1,7,8]. The treatment strategy for hereditary papillary renal cell carcinoma is contingent on the stage and dimensions of the tumours. Progression to metastasis can occur if left untreated. Radical nephrectomy is a commonly employed treatment option for large tumours, whereas tumours measuring less than 3 cm in diameter are generally considered low-grade and are managed with a nephron-sparing surgical approach [1,7,9]. Investigation into the efficacy of MET inhibitors for the treatment of HPRCC is ongoing, with several MET inhibitors currently under investigation in solid tumours [1]. The present article reports a clinical case of a 45-year-old male patient who was diagnosed with hereditary renal cell papillary carcinoma affecting both kidneys, and following the diagnosis, the patient underwent a bilateral radical nephrectomy. To the best of our knowledge, it is the first reported case in Greece and one of a limited number of cases reported worldwide.

Case Presentation

A 45-year-old male patient presented to our medical department with the primary concern of investigating his 8-year history of arterial hypertension. To determine the root cause of the hypertension, an abdominal ultrasound examination was carried out, which revealed the existence of multiple tumours with different sizes in both kidneys. The patient reported a persistent haematocrit level of 54% and haemoglobin level of 16 g/dL since the age of 35 years, resulting in him becoming a voluntary blood donor. No significant symptoms such as haematuria or lumbar pain were reported by the patient. Upon reviewing the patient's family history, a pattern of hereditary papillary renal cell carcinoma was identified, with both the patient's mother and two siblings having undergone nephrectomy for contralateral renal tumours in the past. Given the multiple tumours present in both kidneys and the positive family history, further evaluation in the form of upper and lower abdominal magnetic resonance imaging was recommended for the patient and his two sisters. The imaging results revealed the existence of multiple tumours in both kidneys of the patient, with the largest tumour located in the lower pole of the left kidney,

measuring 9.6 cm in diameter (Figure 1a, b). The architecture of both kidneys was also noted to be altered. No lymph genic or distant metastases were reported. One of the patient's sisters, who resides abroad and is 43 years old, was found to have bilateral nodules with diameters ranging from 1-2 cm, and a biopsy from one nodule of the left kidney confirmed the presence of papillary renal cell carcinoma.

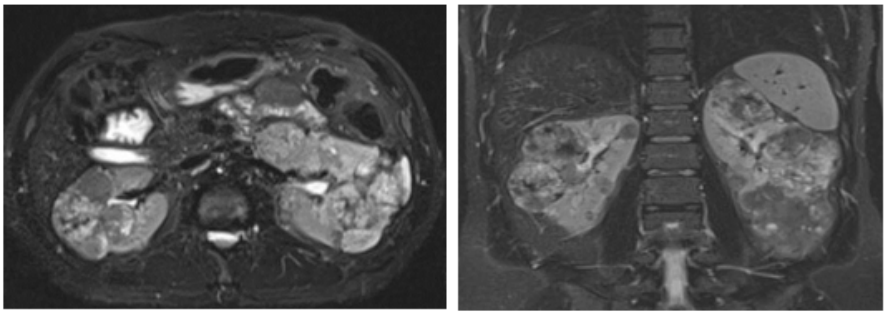

Figure 1: Patient's abdominal T2-weighed MRI revealed the existence of multiple tumours in both kidneys of the patient, with altered architecture a) axial b) coronal.

In light of the above findings, a bilateral nephrectomy was deemed necessary, followed by initiation of dialysis. The renal masses and frozen sections from the margins of the resection were sent for histopathology that showed papillary renal cell carcinoma; grade III (Figure 2a, b). The margins were negative, and there was evidence of invasion of the surrounding perirenal fat of the left kidney. The postoperative course was uneventful and without any complications. The patient is scheduled for transplant evaluation after a 2-year period without any evidence of disease recurrence.

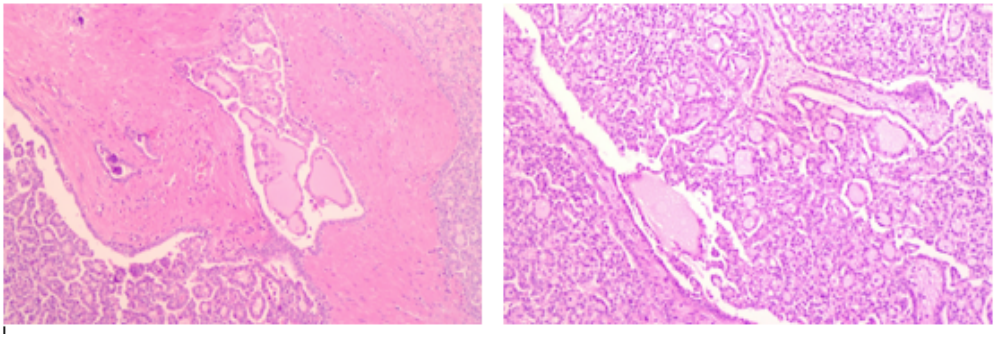

Figure 2: Hematoxylin-Eosin strain, x10 HPF of the patient's papillary renal cell carcinoma, grade III a) tubulopapillary, micro cystic and solid architecture and psammoma bodies, b) papillae with fibro vascular cores.

Discussion

It has been estimated that between 3-5% of all cases of renal cell carcinoma are a part of hereditary cancer genetic syndrome [2]. Hereditary Papillary Renal Cell Carcinoma is a rare and unique autosomal dominant form of renal cancer syndrome, the incidence of which is not clearly defined [4]. The development of HPRCC is caused by germline mutations to the proto-oncogene MET, which is located on chromosome 7q31-34 [5]. These mutations result in the constitutional activation of MET, a tyrosine kinase receptor found on the surface of renal epithelial cells [10]. MET is responsible for encoding the hepatocyte growth factor receptor (HGFR) and plays a crucial role in tumour growth, metastasis, and progression. The mutations in HPRCC activate the tyrosine-kinase (TK) domain of MET, leading to the activation of the HGF/MET pathway, which stimulates cell growth, motility, and proliferation [10,11]. It is worth noting that MET mutations or alterations have also been observed in other types of cancer, including hepatocellular carcinoma, endometrial cancer, breast cancer, gastric cancer, and squamous cell carcinoma of the head and neck [12,13]. Hereditary Papillary Renal Cell Carcinoma is a rare and distinct subtype of hereditary renal cell carcinoma characterized by an increased risk of the development of bilateral or multifocal macroscopic and microscopic papillary renal lesions, without external manifestations [6,8,14,15]. HPRCC is caused by germline mutations in the proto-oncogene MET, located on chromosome 7q31-3. Individuals who carry known or probable pathogenic mutations in the MET gene have a high probability of developing bilateral or multiple renal cell carcinomas, with some

studies suggesting a penetrance rate of over 90% [1]. The onset of HPRCC typically occurs during the fourth to sixth decades of life and can range from an incidental diagnosis to more advanced disease, manifesting with symptoms such as haematuria, abdominal pain, and abdominal masses [10]. Hereditary papillary renal cell carcinomas pose challenges in diagnostic imaging due to their hypo vascular nature and potential for misdiagnosis as cysts. For proper evaluation, it is advised to utilize Magnetic Resonance Imaging or Computed Tomography with contrast enhancement, as ultrasound may not provide adequate visualization. CT and MRI scans demonstrate HPRCC tumours as hypo-enhancing masses, which can be mistaken for cysts. While there are no established screening guidelines, serial cross-sectional imaging every 1-2 years starting at age 30 is commonly recommended for individuals with a documented family history of HPRCC [1,7,8,10,16]. Treatment options for HPRCC include active surveillance, cry ablation, or radiofrequency ablation for smaller tumours with low metastatic potential [10]. Surgical intervention is advised when the largest dimension of the lesion reaches 3cm, and nephron-sparing surgery is utilized where feasible to preserve renal function. In the absence of suitable conditions for nephron-sparing surgery, the choice of partial or radical nephrectomy will depend on the surgeon's discretion [1,7,9]. Currently, there is no established therapy specifically designed to treat HPRCC lesions. However, several studies have explored the potential of targeting MET proto-oncogene, as it is known to play a central role in the development of HPRCC, particularly in patients who harbour activating mutations in the MET gene. The use of MET-targeting agents, such as foretinib, crizotinib, savolitinib, and cabozantinib, has shown varying degrees of efficacy in the treatment of HPRC [1,11,12,17]. For instance, foretinib has demonstrated modest benefits in the treatment of papillary RCC but with higher response rates observed in patients with germline MET mutations [1,14]. In a separate phase III study, savolitinib was found to have numerically higher response rates, overall survival, and progression-free survival compared to sunitinib, with fewer adverse effects [11,12,17]. However, it is not yet clear how patients with germline-MET mutations would respond to savolitinib compared to sunitinib. Additionally, the use of checkpoint inhibitors and immunotherapy in treating non-clear cell RCC is less well studied, but initial results using pembrolizumab and durvalumab have shown promising response rates [1]. Further studies are needed to better understand the potential benefits of these treatments for patients with HPRCC.

Conclusion

In conclusion, Hereditary Papillary Renal Cell Carcinoma is a hereditary renal cell carcinoma that is caused by germline mutations in the proto-oncogene MET. Individuals with known or probable pathogenic mutations in the MET gene must be aware because they have a high probability of developing bilateral or multiple renal cell carcinomas. The proper evaluation of HPRCC requires the use of MRI or CT with contrast enhancement, and treatment options include active surveillance, cryoablation, or radiofrequency ablation for smaller tumours, and surgical intervention for larger tumours. Currently, there is no established therapy specifically designed for HPRCC, but several studies have explored the potential of targeting MET and the use of MET-targeting agents has shown varying degrees of efficacy in the treatment of HPRCC. Further studies are needed to better understand the potential benefits of these treatments for patients with HPRCC.

References

1. Webster BR, Gopal N, Ball MW (2022) Tumorigenesis Mechanisms Found in Hereditary Renal Cell Carcinoma: A Review, Genes. 13: 2122.
2. Wadt KAW, Gerdes AM, Hansen TVO, Toft BG, Friis-Hansen L, et al (2012) Novel germline c-MET mutation in a family with hereditary papillary renal carcinoma, Fam. Cancer. 11: 535-537.
3. Ferlicot S, Just PA, Compérat E, Rouleau E, Tissier F, et al (2021) Clear cell and papillary renal cell carcinomas in hereditary papillary renal cell carcinoma (HPRCC) syndrome: a case report, Diagn. Pathol. 16: 107.
4. Maher ER (2018) Hereditary renal cell carcinoma syndromes: diagnosis, surveillance and management, World J. Urol. 36: 1891-1898.
5. Schmidt L, Duh FM, Chen F, Kishida T, Glenn G, et al (1997) Germline and somatic mutations in the tyrosine kinase domain of the MET proto-oncogene in papillary renal carcinomas, Nat. Genet. 16: 68-73.
6. Courthod G, Tucci M, Maio MD, Scagliotti GV (2015) Papillary renal cell carcinoma: A review of the current therapeutic landscape, Crit. Rev. Oncol. Hematol. 96: 100-112.
7. Schmidt LS, Linehan WM (2016)Genetic predisposition to kidney cancer, Semin. Oncol. 43: 566-574.
8. Freifeld Y, Ananthakrishnan L, Margulis V (2018) Imaging for Screening and Surveillance of Patients with Hereditary Forms of Renal Cell Carcinoma, Curr. Urol. Rep. 19: 82.
9. Dharmawardana P, Giubellino A, Bottaro D (2004) Hereditary Papillary Renal Carcinoma Type I, Curr. Mol. Med. 4: 855-868.
10. Mustafa S, Jadidi N, Faraj SF, Rodriguez R (2012) Case of hereditary papillary renal cell carcinoma, J. Community Hosp. Intern. Med. Perspect. 1: 9468.
11. Miyata Y, Asai A, Mitsunari K, Matsuo T, Ohba K, et al (2014) Met in Urological Cancers, Cancers. 6: 2387-2403.
12. Rhoades Smith KE, Bilen MA (2019) A Review of Papillary Renal Cell Carcinoma and MET Inhibitors, Kidney Cancer. 3: 151-161.
13. Tovar EA, Graveel CR (2017) MET in human cancer: germline and somatic mutations, Ann. Transl. Med. 5: 205-205.
14. Carlo MI, Hakimi AA, Stewart GD, Bratslavsky G, Brugarolas J, et al (2019) Familial Kidney Cancer: Implications of New Syndromes and Molecular Insights, Eur. Urol. 76: 754-764.
15. Haas NB, Nathanson KL (2014) Hereditary Kidney Cancer Syndromes, Adv. Chronic Kidney Dis. 21: 81-90.

16. Schmidt LS, Nickerson ML, Angeloni D, Glenn GM, Walther MM, et al (2004) Early Onset Hereditary Papillary Renal Carcinoma: Germline Missense Mutations In The Tyrosine Kinase Domain Of The Met Proto-Oncogene, J. Urol. 172: 1256-1261.

17. Mikhaylenko DS, Klimov AV, Matveev VB, Samoylova SI, Strelnikov VV, et al (2020) Case of Hereditary Papillary Renal Cell Carcinoma Type I in a Patient With a Germline MET Mutation in Russia, Front. Oncol. 9: 1566.