

## Oncology

## Tubulocystic renal cell carcinoma with poorly differentiated foci and loss of fumarate hydratase: A case report

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## ARTICLE INFO

## Keywords:

Tubulocystic  
Renal cell carcinoma  
Poorly differentiated foci  
Fumarate hydratase

## ABSTRACT

Tubulocystic renal cell carcinoma (RCC) is one of the newly recognized subtypes of RCC. It has a unique cystic morphology and indolent behavior. During the last decade, few studies have been published describing tubulocystic RCC with poorly differentiated foci. A subset of these cases are associated with loss of fumarate hydratase which is a characteristic feature of hereditary leiomyomatosis and renal cell carcinoma-associated RCC. However, these two entities represent two distinct subtypes of RCC in the recent WHO Classification of kidney tumors. Herein, we are describing a rare case of tubulocystic renal cell carcinoma with poorly differentiated foci and loss of fumarate hydratase.

## Introduction

Tubulocystic renal cell carcinoma (RCC) is a rare distinct subtype of renal cell carcinoma which is recently incorporated in the 2016 world health organization (WHO) classification of tumors of the kidney. The majority of these tumors have indolent behavior with low metastatic potential.<sup>1</sup> However, few cases of tubulocystic RCC with poorly differentiated foci or high grade have been described. Tubulocystic RCC with poorly differentiated foci was first described in 2013 by Al-Hussain et al. as a series of 3 cases, two of which had trisomy of chromosome 17.<sup>2</sup> A subsequent study by Smith et al.<sup>3</sup> found that a subset of tubulocystic RCC with poorly differentiated foci are associated with loss of fumarate hydratase which is a hallmark of hereditary leiomyomatosis and renal cell carcinoma-associated renal cell carcinoma.<sup>3</sup> Such finding has clinical implication and requires further workup including genetic counseling. Recognition of this finding as well as accurate diagnosis of this type of RCCs are paramount, not only because of their potential aggressive behavior but also because of consequences of the loss of fumarate hydratase.

## Clinical presentation

A 45-year-old male with history of diabetes mellitus, hypertension,

and EX-Smoker and with no family history of RCC. He presented with left flank pain for the last two years. And referred to our hospital in April 2018. Computed Tomography Scan showed 24 x 13.9 x 13.0 cm multiloculated cystic mass arising from the posterior aspect of the left kidney with few thin septa and multiple hyper enhancing nodules located along some of the septa; and compatible with a Bosniak 3 (indeterminate) cyst (Fig. 1a). The patient underwent left robotic radical nephrectomy. Gross examination showed a cystic tumor measuring 24.0 x 14.0 x 13.0 cm involving the posterior aspect of the kidney. Cut sections revealed a well circumscribed cystic tumor composed of multilocular cysts with smooth lining filled with clear fluid (Fig. 1b). Multiple yellow-tan solid areas were identified, the largest measuring 2.0 cm in maximum dimension. Microscopically, the tumor showed variable cysts lined by single layer of eosinophilic cells containing prominent nucleoli (WHO/ISUP grade 3) (Fig. 2a (L)). Also, there were poorly differentiated foci consisting of cribriform growth with focal papillary formation (Fig. 2b (R)). These foci had cells with eosinophilic cytoplasm and large prominent inclusion-like eosinophilic nucleoli with perinucleolar halo (Fig. 2b (L)). The tumor was limited to the kidney without renal sinus or perinephric fat invasion. Immunohistochemical stains were performed on a Ventana Benchmark Ultra autostainer (Ventana Medical System, Tucson, AZ). The tumor cells were positive for Cytokeratin and AMACR (Ventana; prediluted). The tumor cells were negative for Cytokeratin 7

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<https://doi.org/10.1016/j.eucr.2020.101236>

Received 28 April 2020; Accepted 30 April 2020

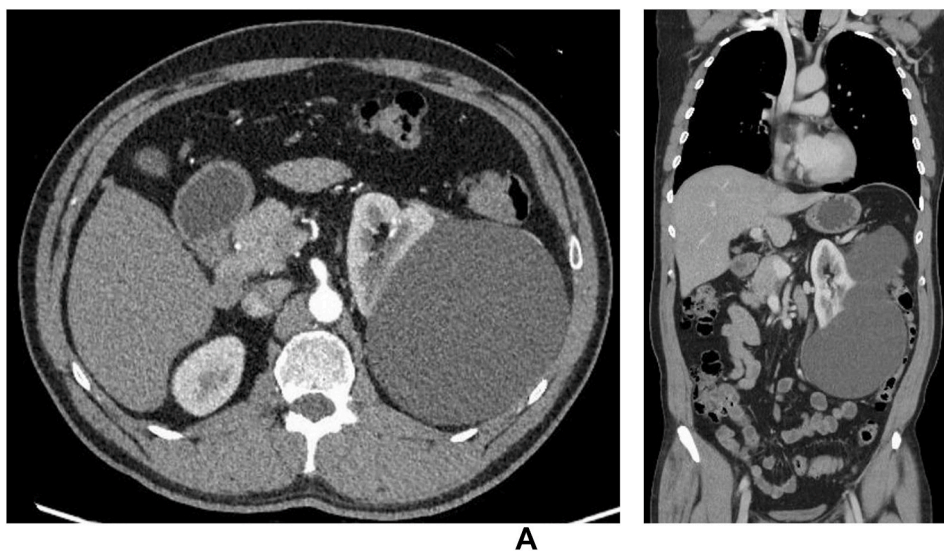
Available online 28 May 2020

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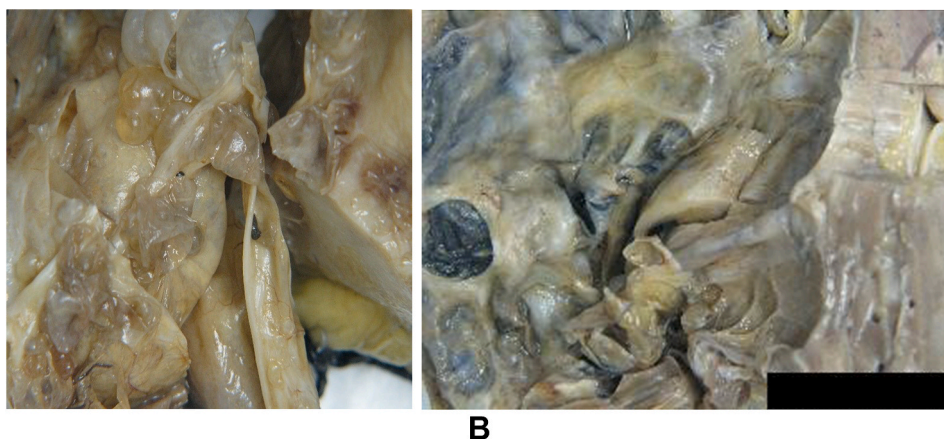
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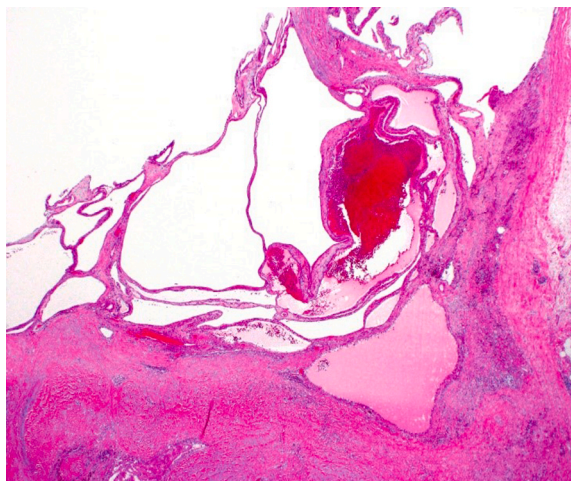
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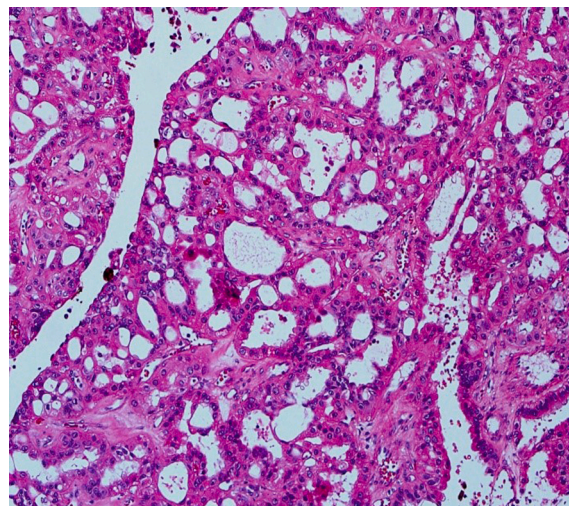
**Fig. 1a.** CT Scan showing large cystic mass involving left kidney.



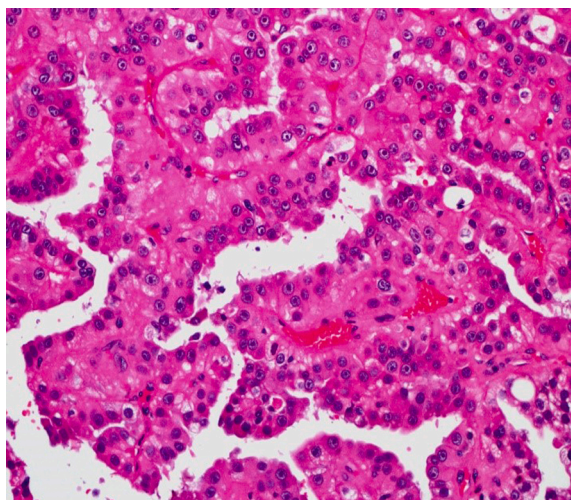
**Fig. 1b.** Gross photograph of the tumor with multiple cysts.



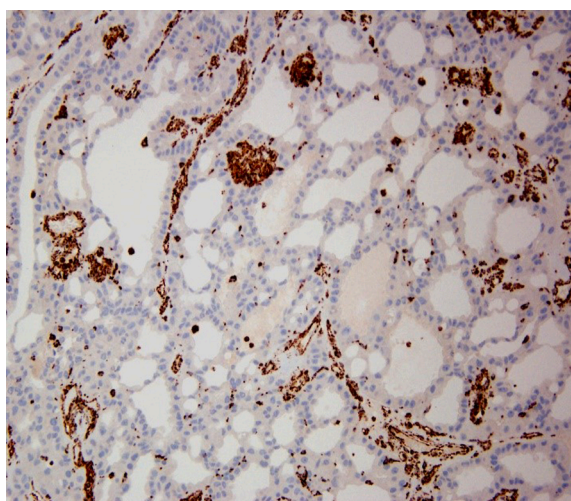
**Fig. 2a (L).** Tubulocystic carcinoma showing multiple cysts lined by eosinophilic cells.



**Fig. 2a(R).** Poorly differentiated area with cribriform morphology.



**Fig. 2b(L).** Papillary component with obvious large prominent inclusion-like eosinophilic nucleoli with perinucleolar halo.



**Fig. 2b(R).** Immunohistochemical stain for fumarate hydratase with loss of expression.

(Ventana; prediluted), TFE3, CD10, and CA-IX (Ventana; prediluted), fumarate hydratase (J-13, Santa Cruz Biotechnology, Santa Cruz CA, 1: 200) was lost (Fig. 2b (R)). The diagnosis was tubulocystic RCC with poorly differentiation foci and loss of fumarate hydratase with a comment that fumarate hydratase loss could either be sporadic or germline as seen in hereditary leiomyomatosis and associated renal cell carcinoma. Therefore, clinical correlation and genetic workup are warranted. The patient had no evidence of recurrence or metastasis twenty-four months after the surgery.

## Discussion

Tubulocystic RCC constitutes <1% of all renal carcinomas with male predominance.<sup>1</sup> It is well-circumscribed tumor with characteristic spongy cut surface. Microscopically, it consists of variable-sized tubules and cysts separated by thin septae, which are lined by single layer of flat, hobnail, cuboidal/columnar epithelial cells. The cells have abundant eosinophilic cytoplasm with round nuclei and prominent nuclei (WHO/ISUP grade 3). Most of tubulocystic RCCs have indolent behavior with low metastatic potential and rare recurrence.<sup>1</sup> Sarungbam et al.<sup>4</sup> studied nine cases of pure tubulocystic RCC by targeted next generation sequencing and fluorescence in situ hybridization for X and Y

chromosomes, all showed combined losses at chromosome 9 and gains at chromosomes 17 with loss of Y chromosome in 5 of 5 cases.<sup>4</sup> This supports that pure tubulocystic RCC as defined by World Health Organization represent a distinct entity. Recently, cases of tubulocystic RCCs with poorly differentiated foci or high grade have been reported.<sup>2,5</sup> Al-Hussain et al.<sup>2</sup> reported 3 cases of tubulocystic RCCs with poorly differentiated foci that increased the risk of aggressive behavior.<sup>2</sup> Similarly, Zhao et al.<sup>5</sup> reported two cases of tubulocystic RCC with poorly differentiated foci; one of which had metastasis in the pelvic cavity.<sup>5</sup> However, Smith et al.<sup>3</sup> reported 29 cases of tubulocystic RCC with poorly differentiated foci, of which 16 (55%) had loss of fumarate hydratase by immunohistochemistry with strong diffuse nucleocytoplasmic positivity for S-(2-succino)-cysteine (2SC) in 14 of 14 cases.<sup>3</sup> In addition, 8 of 29 cases had strong diffuse positivity for 2SC with variable positivity for fumarate hydratase, of which 3 revealed fumarate hydratase mutation by next generation sequencing.<sup>3</sup> Most of tubulocystic RCCs with poorly differentiated foci have a characteristic nucleus as seen in our case in the form of large nuclei with prominent inclusion-like eosinophilic nucleoli reminiscent of nuclear features described in hereditary leiomyomatosis and renal cell carcinoma-associated renal cell carcinomas. However, a sporadic form does exist and the provisional diagnostic term for such tumors is fumarate hydratase-deficient RCC. Now, the intriguing question is whether tubulocystic RCC can have poorly differentiated foci in which fumarate hydratase is frequently lost or not. Moreover, tubulocystic pattern is one of the morphological patterns of hereditary leiomyomatosis and renal cell carcinoma-associated renal cell carcinoma. Therefore, we support the provisional diagnostic term of fumarate hydratase-deficient RCC for cases of tubulocystic carcinoma with poorly differentiated foci and loss of fumarate hydratase in which history cannot be reliably ascertained. This is also in line with the 2016 WHO classification of tumors of the kidney that restricts the term tubulocystic RCC to tumors with the classic histological features.

## Conclusion

In summary, we are reporting a rare case of tubulocystic RCC with poorly differentiation foci and loss of Fumarate Hydratase. Pathologists should pay attention to the characteristic nucleoli of such tumors because these definitely require further workup and genetic testing in addition to their aggressive behavior in comparison to pure tubulocystic RCC.

## Funding sources

The author(s) received no financial support for the research, authorship, and/or publication of this article.

## Author contributions

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Drafting the case report: Noor Nabi Junejo, Turki O. Al-Hussain

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## Declaration of competing interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Acknowledgement

The authors would like to thank Dr. Jonathan I. Epstein (The Johns Hopkins Hospital) for his expert opinion in this case.

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