


Succinate Dehydrogenase-Deficient Renal Cancer Featuring Fructose-1,6-Biphosphatase Loss, Pyruvate Kinase M2 Overexpression, and SWI/SNF Chromatin Remodeling Complex Aberrations: A Rare Case Report

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[Correction added on 04 Jun 2021, after first online publication: The affiliation of Dr. Kowalik has been updated.]

ABSTRACT

Succinate dehydrogenase (SDH)-deficient renal cancer is a rare renal cancer subtype recently accepted by the World Health Organization as a unique subtype of renal cell carcinoma (RCC). Here we report a case of 17-year-old man. The detailed evaluation indicated occurrence of the SDHB-deficient RCC. The genetic testing revealed no germline mutation in *SDH* genes. Immunohistochemistry showed SDHB deficiency, overexpression of pyruvate kinase M2 and dramatic downregulation of fructose-1,6-bisphosphatase metabolic enzymes, and unaltered levels of phosphorylated AMP-activated

protein kinase and mammalian target of rapamycin. Strong upregulation of INI1 and BRG1 and overexpression of BAF180, subunits of SWI/SNF ATP-dependent chromatin remodeling complex, were also found. The identified tumor pathologically did not resemble clear cell renal cell carcinoma (ccRCC), but some metabolic alterations are common for both cancer types. Thus, we postulate that the phenotypical differences between ccRCC and SDHB-deficient RCC may be related to distinct molecular and metabolic alterations. *The Oncologist* 2021;26:e1652–e1655

Implications for Practice: Succinate dehydrogenase (SDH)-deficient renal cell carcinoma (RCC) is a rare renal tumor occurring even in young patients. Until now, in all described and genetically tested cases, mutations and deletions in *SDH* genes have been found. This article describes SDHB-deficient RCC without any germline mutations in *SDH* genes. Therefore, genetic analysis for germline mutations in *SDH* genes in SDH-deficient RCC, especially in young individuals, should be strongly recommended, although as of now it is not obligatory. This knowledge will allow improvement of patient monitoring including both disease recurrence and new cancer appearance.

BACKGROUND

Succinate dehydrogenase (SDH)-deficient renal cell carcinoma (RCC) was originally described in 2004. In 2016 it was

accepted by the World Health Organization as a separate rare RCC subtype representing around 0.05%–0.2% of all

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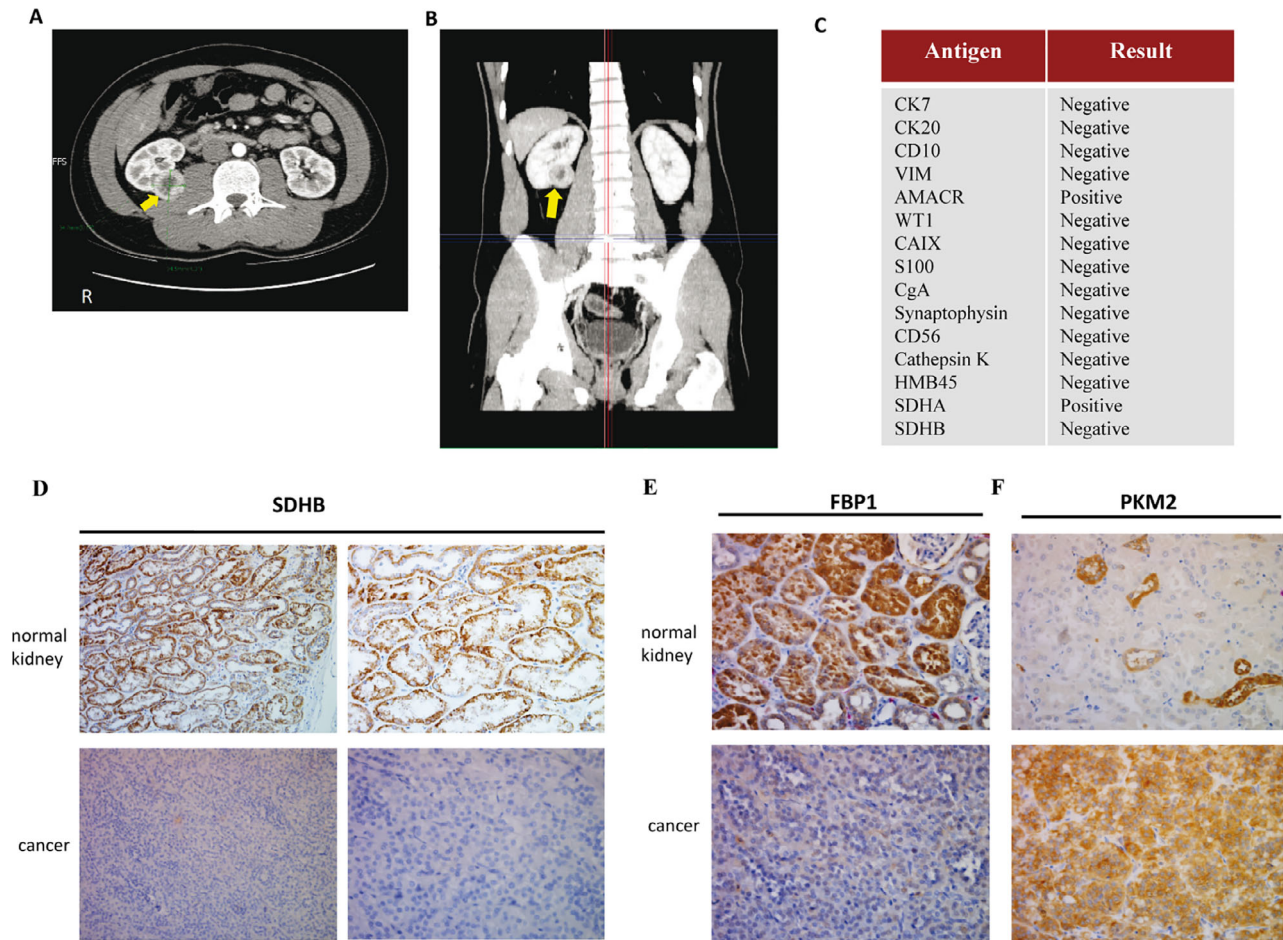


Figure 1. SDHB-deficient renal cell carcinoma (RCC) in a 17-year-old man is characterized by metabolic aberrations related to glycolysis and Krebs cycle. **(A, B):** Abdominopelvic computed tomography scan in transversal **(A)** and coronal **(B)** plan. The arrowheads indicate the 35 mm renal mass in the right kidney. **(C):** Standard immunohistochemistry (IHC) summary. **(D):** Immunostaining for SDHB. Staining for SDHB was positive in normal kidney tissue (upper panel) and negative in cancer cells (lower panel), indicative of the SDHB deficiency in this type of cancer. Magnification, $\times 20$ (left panel) and $\times 40$ (right panel). **(E):** IHC for glycolysis enzyme FBP1, which controls the proper glycolysis flux in the cell, indicates strong impairment of glycolysis in SDHB-deficient RCC. **(F):** IHC for glycolysis enzyme PKM2 indicates strong accumulation of this enzyme in the cancer cells, suggesting strong metabolic alterations in SDHB-deficient RCC. Magnification for FBP1 and PKM2, $\times 40$. Abbreviations: FBP1, fructose-1,6-bisphosphatase; PKM2, pyruvate kinase M2; SDHA, succinate dehydrogenase A; SDHB, succinate dehydrogenase B.

RCCs [1]. Around 75% of all patients with SDH-deficient RCC carry a germline mutation in the gene encoding the SDHB subunit of the SDH complex, which is composed of four proteins, SDHA, SDHB, SDHC, and SDHD. Mutations in the *SDHA*, *SDHC*, and *SDHD* genes are less frequent. Until now only 59 SDH-deficient RCC cases have been described [2–6]. Patients' ages at diagnosis ranged from 14 to 76 years. Only seven cases were reported for patients aged younger than 20 years [2]. Patients harboring *SDH* mutations have a lifetime risk to develop RCC of around 14% and are also predisposed to develop paragangliomas, pheochromocytomas, and gastrointestinal stromal tumors. Usually, SDH-deficient RCC is diagnosed as a low-grade tumor with a good prognosis. The metastasis rate is approximately 33% [2].

SDH, the succinate dehydrogenase complex, is involved in both the Krebs cycle (tricarboxylic acid cycle) and the electron transport chain. SDH enables conversion of succinate to fumarate [7]. SDH loss leads to overaccumulation of

metabolic intermediates, that is, succinate, a signaling molecule in processes involved in inflammation and cancer and that affect chromatin status [8]. Some RCC types, such as clear cell renal cell carcinoma (ccRCC), are characterized by aberrations in the switch/sucrose non fermentable (SWI/SNF) chromatin remodeling complex (CRC), which is involved in the control of gene expression and cancer development via chromatin structure [9].

CASE PRESENTATION

A 17-year-old man, otherwise healthy, reported pain on the right side of his abdomen lasting a few weeks. No gastrointestinal stromal tumor, paraganglioma, or pheochromocytoma was reported in his family. On examination all routinely tested parameters were normal. Ultrasonography examination showed a pathological mass in the right kidney.

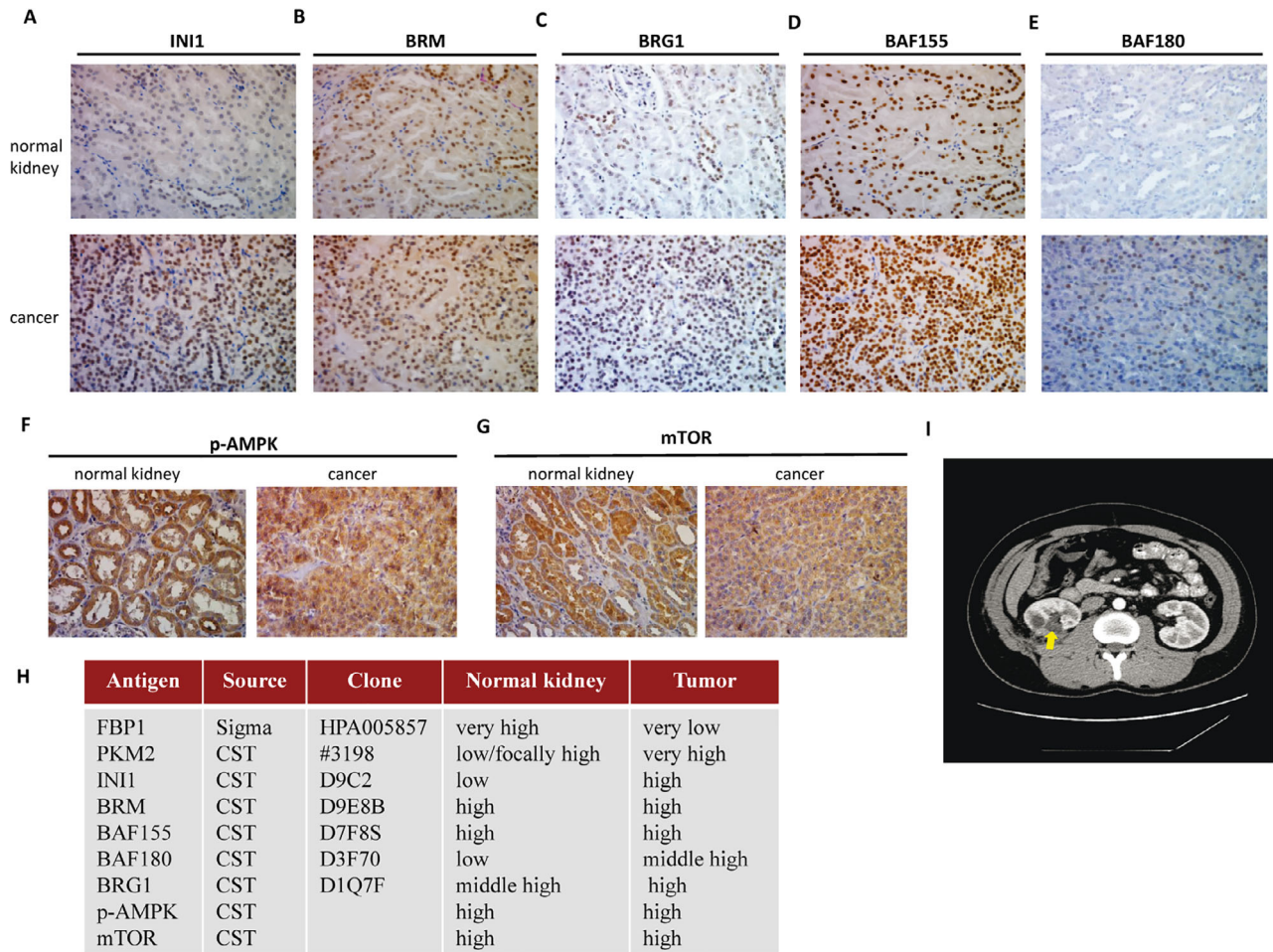


Figure 2. Overexpression of some subunits of SWI/SNF chromatin remodeling complex characterizes the succinate dehydrogenase B (SDHB)-deficient renal cell carcinoma (RCC) case subjected to the partial nephrectomy. **(A–E):** Immunohistochemistry (IHC) for main SWI/SNF subunits in normal kidney tissue and cancer, indicating overaccumulation of INI1 protein in SDHB-deficient RCC cells **(A)**, similar levels of BRM in healthy kidney tissue and SDHB-deficient RCC cells **(B)**, overaccumulation of BRG1 in SDHB-deficient RCC cells **(C)**, similar levels of BAF155 in healthy kidney tissue and SDHB-deficient RCC cells **(D)**, and overaccumulation of BAF180 in SDHB-deficient RCC cells **(E)**. **(F, G):** IHC staining indicated similar levels of p-AMPK **(F)** and mTOR **(G)** in normal and SDHB-deficient cancer cells. **(H):** The antibody description and signal strength assessment used in normal kidney and tumor. **(I):** Abdominopelvic computed tomography scan in transversal plan 1 year after surgery; arrowhead indicates the previous tumor site. Abbreviations: CST, cell signaling technology; FBP1, fructose-1,6-bisphosphatase; mTOR, mammalian target of rapamycin; p-AMPK, phosphorylated AMPK; PKM2, pyruvate kinase M2.

Computed tomography (CT) of the abdomen and pelvis (Fig. 1A) with contrast material confirmed the presence of a solid mass (diameter 35 mm) at the back-lower pole of the right kidney (Fig. 1B). CT scan of the chest revealed no evidence for metastatic cancer. In April 2017 a partial right nephrectomy was performed. The pathological examination revealed the occurrence of SDH-deficient RCC classified as International Society of Urological Pathology nucleolar grade 2. The standard immunohistochemistry (Fig. 1C) indicated negative SDHB staining in cancer cells (Fig. 1D).

The genetic test for germline mutation in *SDH* was performed; DNA was isolated from blood samples and examined using Ion Torrent next-generation sequencing (Thermo Fisher Scientific, Waltham, MA). The sequencing for exon panel of *VHL*, *RET*, *SDHA*, *SDHB*, *SDHC*, *SDHD*, *SDHAF1*, *SDHAF2*, and *MAX* was successful with 100% coverage at $\times 20$ coverage depth. No germline mutations or deletions

were found. The exons not covered by the panel were additionally sequenced using the Sanger method.

Given the occurrence of metabolic alterations in another RCC (ccRCC) [9], we examined the abundance of fructose-1,6-bisphosphatase (FBP1) (Fig. 1E) and pyruvate kinase M2 (PKM2) (Fig. 1F) proteins in this case. We found nearly complete loss of FBP1 and strong overexpression of PKM2 in cancer cells compared with healthy tissue.

In ccRCC, mutations and aberrations of SWI/SNF CRC occur [9, 10]. Thus, we examined the abundance of the main SWI/SNF CRC subunits (INI1, BRM, BRG1, BAF155, and BAF180; Fig. 2A–E). Whereas for BRM and BAF155 no alterations were observed, BRG1 ATPase, INI1, and BAF180 were overexpressed in SDHB-deficient cancer cells. Subsequently, we tested the abundance of activated AMP-activated protein kinase (AMPK) (phosphorylated at Tyr172) and mammalian target of rapamycin (mTOR) kinase, as ccRCC exhibits mTOR hyperactivation and loss of AMPK activity.

No differences in AMPK activation (Fig. 2F) and mTOR abundance (Fig. 2G) were found, further indicating that SDHB-deficient RCC (Fig. 2H) and ccRCC are characterized by different metabolic alterations.

At follow-up with the patient 1 year after surgery, no evidence of disease recurrence was found (Fig. 2I).

DISCUSSION

SDHB deficiency is usually caused by either point mutation or deletion in the *SDHB* gene. Mutations in other *SDH* genes may also result in SDHB deficiency.

Here we describe, for the first time, the SDHB-deficient RCC without germline point mutations or deletions in any *SDH* genes. Thus, the existence of *SDH* mutations seems not to be an obligatory factor for occurrence of this cancer type. This observation is consistent with higher frequency of particular *SDHB* point mutations in the population than the occurrence of SDHB-deficient cancers [11].

The studied case featured FBP1 loss and PKM2 overexpression, suggesting the metabolic switch to aerobic glycolysis known as the Warburg effect [12]. Observed metabolic disorders partially resembled these in ccRCC (FBP1 loss, tricarboxylic acid impairment); however, SDHB-deficient RCC accumulates succinate, whereas ccRCC accumulates fatty acids.

In contrast to the loss of SWI/SNF CRCs observed in ccRCC, here we found overexpression of BRG1, INI1, and BAF180 subunits. Some SWI/SNF CRC subunits have been reported as tumor suppressors; for example, transient INI1 restoration in ccRCC caused downregulation of metastasis-

related genes [9]. Other subunits may act as oncogenes; for example, overexpression of BRM ATPase correlates with increased expression of chemoresistance-related genes in adenoid cystic carcinoma [12]. Thus, we postulate that the differential aberrations in SWI/SNF CRC could be related to different aggressiveness in ccRCC and SDHB-deficient RCCs. Because of overexpression, the protective function of INI1 and BRG1 subunits may be more pronounced in the SDHB-deficient RCC; however, it needs to be confirmed in a larger group of patients. Additionally, in the SDHB-deficient tumor neither overexpression of mTOR nor loss of AMPK activity was found, confirming the different metabolic alterations in ccRCC and SDHB-deficient RCC.

Conclusion

SDHB-deficient RCC primary tumor is characterized by metabolic aberrations, including FBP1 loss, PKM2 overexpression, and overaccumulation of some SWI/SNF CRC subunits. Loss of SDHB is not necessarily caused by mutations in *SDH* genes.

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DISCLOSURES

The authors indicated no financial relationships.

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