JCSMICR
ISSN 2837-7567

Journal of Clinical Studies and Medical Images, Case Reports

Case Report

Volume 1, Issue 3

Received: June 03, 2023
Published: June 27, 2023

DOI: 10.55920/2837-7567/1015

Succinate dehydrogenase (SDH) deficient renal cell carcinoma (RCC)

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Abstract

Succinate dehydrogenase (SDH) deficient renal cell carcinoma (RCC) are recently described uncommon renal tumors that typically present in younger patients. SDH mutations are known for tumorigenesis and are often associated with hereditary paragangliomas, pheochromocytomas, and gastrointestinal stromal tumors. Ours is a case of 31-year-old male who presented with retroperitoneal paragangliomas four years prior to his SDH deficient renal cell carcinoma with no significant family history. Magnetic resonance imaging (MRI) revealed a
3.9 cm mass in the right kidney. A Radical nephrectomy was performed, and the patient had an uneventful recovery. Microscopy showed a well circumscribed tumor with nested and tubular architecture. The tumor cells were positive for PAX8, AMACR, focal CD10, with no loss of Fumarate hydrogenase (FH) and negative for SDHB, CAIX, CK7, CD117. The importance of diagnosing this entity lies in its favorable prognosis and hereditary predisposition to other disease entities.

Intoduction

Succinate dehydrogenase (SDH)–deficient renal cell carcinoma (RCC) is a recently recognized distinct subtype of RCC in molecular defined renal carcinomas in the 2022 World Health Organization classification [1]. It is rare (0.05%–0.2% of all renal carcinomas) and commonly presents in young adults with an average age of 37 years [2]. The four subunits of succinate dehydrogenase (SDHA, SDHB, SDHC, and SDHD), SDHB mutation is most associated with renal cell carcinomas [1,3]. Other than RCC SDHB mutations are associated with hereditary predisposition to paraganglioma, pheochromocytoma, pituitary adenoma, gastrointestinal stromal tumor [2].

Case Presentation

Clinical history and microscopic description

We are presenting a case of 31-year-old male who initially presented to emergency department in August 2016 with left flank pain and on Computed tomography (CT) anterior posterior (AP) showed right posterior lymphadenopathy and left renal hypodensity. He was subsequently treated for pyelonephritis. Follow up CT in September 2016 showed resolution of abscess/hematoma, but persistence of lymphadenopathy. He was diagnosed with multifocal retroperitoneal paraganglioma on 10/24/2017 on lymph node biopsy which was subsequently excised along with incomplete debulking on 5/9/2018. Genetic studies were ordered which showed pathogenic variant (mutation) in the SDHB gene. Follow up CT after surgery in July 2018.

showed residual disease, with lesion measuring 1.8 x1.6 cm in right kidney suspicious for metastasis vs new primary. The lesion was stable till July 2019. Follow up was scheduled for November 2019 but the patient was lost to follow up. Patient again presented on 2/22 and Magnetic resonance imaging (MRI) was performed which showed an enhancing 3.1 x 2.5cm right renal mass. Patient was planned for partial nephrectomy.

We received a partial nephrectomy specimen which showed a 4.1 x 2.6 x 2.2 cm tan-white, bulging, lobulated well-circumscribed mass. The mass abuts the inked external surface and was
0.1 cm from the parenchymal margin. The remaining uninvolved kidney parenchyma was tan, brown and unremarkable.

Microscopically, Hematoxylin and Eosin (H & E) slide showed a well circumscribed lesion (figure 1) with tumor cells arranged in sheets and compact nests of bland cells with eosinophilic to pale bubbly cytoplasm (fig 2). The eosinophilic cytoplasm, with pale, bubbly appearance, lacks the fine homogeneous granularity of oncocytoma (fig 3). A characteristic, but inconstant feature is the presence of cytoplasmic inclusions containing eosinophilic or pale flocculent material (fig 3). The cells also lack prominent cell borders, like in chromophobe RCC. The tumors commonly contain microcysts filled with pale eosinophilic fluid. On Immunohistochemistry (IHC), loss of expression of SDHB was observed with positive internal control in non- neoplastic cells (fig 4).

Discussion

Succinate dehydrogenase (SDH) is a mitochondrial enzyme that plays a role in both the citric acid cycle and Krebs cycle [4]. This enzyme is composed of 4 protein subunits including: SDHA, SDHB, SDHC, and SDHD [5]. If germ line mutations occur in genes encoding for any of these four subunits, individuals can be susceptible to hereditary dis-

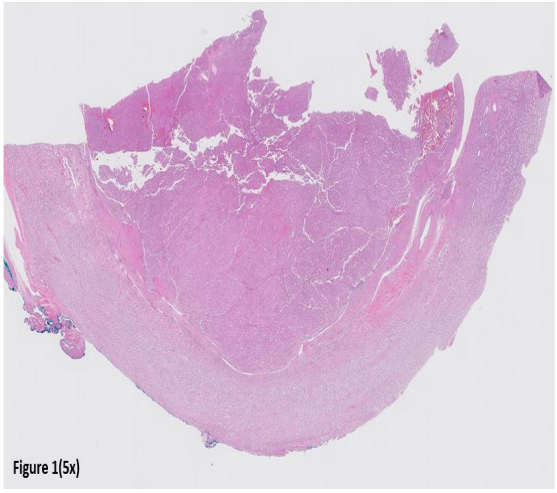

***Figure 1**: Hematoxylin and Eosin staining shows well circumscribed tumor.*

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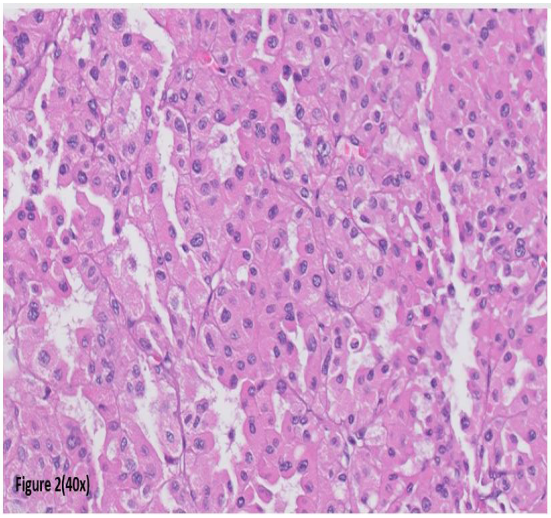
Citation: *Muhammad abdulwaasey. Primary Bladder Osteosarcoma: A Rare Entity with an Unfavorable Prognosis. Jourl of Clin Stud and Med Imag, Cas Rep. 2023; 1(3): 1015.



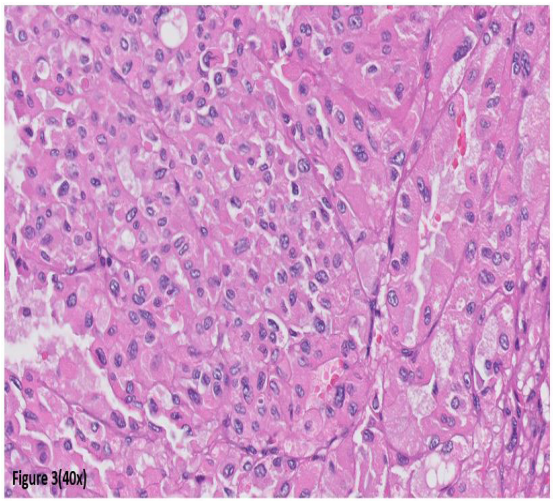


***Figure 2 & 3**: Hematoxylin and Eosin staining shows tumor cells with eosinophilic to pale, bubbly cytoplasm containing flocculent material in cytoplasm (40x).*

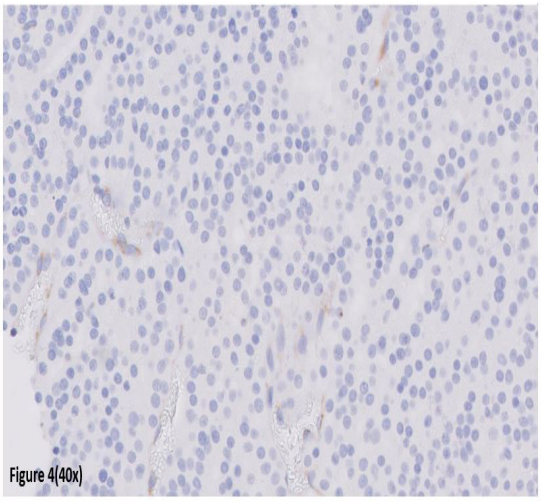


***Figure 4**: Loss of expression of SDHB with positive internal control in non-neoplastic cells (40 x).*

ease such as gastrointestinal stromal tumors, pituitary adenomas, paragangliomas, pheochromocytomas, and renal cell carcinomas.5 Quite recently, the genes which encode for the subunits have been found to be tumor suppressor genes [6]. When a double-hit inactivation occurs in any one of these genes, the SDH enzyme becomes unstable ultimately leading to the degradation of the SDHB subunit [2]. Thus, there is a downregulation of SDH and a resulting accumulation of succinate. This buildup of succinate is believed to have an oncogenic-like signal, as when succinate travels from the mitochondria to the cytosol it inhibits HIF-alpha prolyl hydroxylase (PHD) [7]. This inhibition results in the stabilization of HIF-1alpha in normoxic environments [7]. Therefore, this downstream effect of succinate serves as a catalyst to tumor formation/progression by increasing the gene expression of DNA encoding metastasis, angiogenesis, and glycolysis [7].

SDH deficient RCC is rare, comprising up to only 0.2% of all RCC. There is a slightly higher predominance in men of 1.75:1.8 While SDH deficient RCC has been diagnosed in a wide age range, the median age of diagnosis is ~35 years old [8,9]. Around 75% of SDH deficient RCC is unipolar [9]. Macroscopically, SDH deficient RCC usually presents as a well circumscribed mass ranging from a tan - red color and possible cystic lesions [8,9]. While prognosis with a partial or full nephrectomy is favorable if found in the early stages, diagnoses made in the later stages are poor due to the high rate of malignancy (~70%) [8,9].

Differential diagnoses for SDH deficient RCC include: oncocytoma, chromophobe renal cell carcinoma, eosinophilic variant clear cell carcinoma, hereditary leiomyomatosis, and papillary renal cell carcinoma to name a few [8]. While upon initial analyses such diseases may seem similar, closer inspection of the histology, IHC, and clinical history can help differentiate SDH deficient RCC from similarly presenting conditions [7,8,9]. In particular, SDH deficient RCC has the hallmark presentation of flocculant eosinophilic cytoplasm seen histologically and negative SDHB IHC staining [9].

The patient presented in this case fits the current profile of an individual diagnosed with SDH deficient RCC well, thus adding to the credibility of observations made in previous studies.

However, where this case differs is that this patient has a noted history of multifocal retroperitoneal paraganglioma. This novelty echoes the idea that specific germline mutations link the SDH deficient diseases; implicating that further research should be conducted on the genetic profiles of similar individuals and their families to gain a better understanding on the various SDH gene mutations and their effects on the enzyme's subunits and function. The IHC stain panel in this case yielded the following results: Pax8 (+), AMACR (+), CD10 (+; focal), SDHB (-), CAIX (-), CK7 (-), CD117 (-), and FH (-; no loss). This set of IHC staining differed from the standard stains completed in other studies, leading to the possibility of gaining further insight on the pathophysiology of SDH deficient RCC and being able to diagnose this cancer more accurately from similarly presenting differentials [2,8-10].

Conclusion

While SDH deficient RCC has a low prevalence and a good prognosis, research into this case is important to treat cases in later stages, raise awareness to better/quickly diagnosis cases.

Additionally, delving deeper into the pathophysiology will allow better understanding of the various diseases linked to SDH gene family mutations; thus, potentially allowing for the development of highly accurate genetic screening, individualized treatment, and better prognoses.

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