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Case Report

A New Mutation Site of Succinate Dehydrogenase-Related Carney-Stratakis Syndrome: A Case Report

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Abstract

Carney-Stratakis Syndrome (CSS), first described in 2002 [1], encompasses Gastrointestinal Stromal Tumors (GISTs) and Paragangliomas (PGLs) and has autosomal dominant inheritance with incomplete penetrance [2]. Germline mutations of Succinate Dehydrogenase (SDH) complex subunits and consequent SDH functional deficiency have been identified as responsible for CSS [3]. Here, we present a case with a new mutation site in SDHB that has not yet been reported.

Keywords: Carney-Stratakis Syndrome; Succinate Dehydrogenase; Gene Mutation

Introduction

CSS is a rare disease comprising PGLs and GISTs, which frequently appear in young and middle-aged women [4]. Mutations in SDHx (SDHA, B, C and D) are the main cause of CSS. The SDH complex, located in the inner mitochondrial membrane, comprises 4 subunits (SDHA, B, C and D) and two assembly factors (SDHAF1 and SDHAF2) [5]. SDH deficiency, regardless of the affected subunit, leads to instability of the complex and loss of expression of SDHB, which is unstable in its monomeric form [6]. For this reason, Immunohistochemistry (IHC) for SDHB has been shown to be a tractable surrogate marker for SDH deficiency (IHC for SDHB triages genetic testing of SDHB, SDHC, and SDHD in paraganglioma-pheochromocytoma syndromes).

Family history and tumor history should be fully understood in patients with SDHx deficiency. Genetic testing is necessary for patients with loss of SDHx or CSS expression and their family members (beyond first-degree relatives). In patients with suspected CSS and in whom genetic testing is not available, IHC should be performed. It is also useful to measure the plasma concentration of catecholamines and their metabolites to determine whether patients need to undergo genetic testing [7].

Case Report

A 29-year-old woman was admitted to the People's Hospital of Zhengzhou University (Henan Provincial People's Hospital) on October 28, 2021, with a chief complaint of hypertension for 3 years, and a retroperitoneal tumor was discovered 1 month prior to admission. The patient's blood pressure increased for 3 years without any clinical manifestations. During this period, she went to the hospital for intermittent examination; no abnormality was found on imaging, and no treatment was administered. A month ago, CT showed a lump in the retroperitoneal area. There was no previous medical history or family history of malignant tumors. She was given a preliminary examination on the first day after admission. The laboratory data revealed that the patient had normal routine blood test results, hepatic function, renal function and coagulation function. Serum levels of CA19-9 (27.19 U/ml), CEA (1.39 ng/ml), and CA-125 (16.58 U/ml) were all within the normal range. The serum levels of 3-methoxynorepinephrine and 3-methoxyepinephrine were 258.62 pg/ml and 21.78 pg/ml, respectively. Abdominal contrast-enhanced CT showed irregular soft tissue of approximately 6 cm in the retroperitoneum, with obvious enhancement in the arterial phase and a decrease in the venous phase (Figure 1A). In addition, a 3 cm gastric submucosal tumor was found, with moderate, heterogeneous enhancement (Figure 1B). After admission, the patient was given a large amount of fluid to expand the blood volume to prevent drastic changes in blood pressure during the operation. Thirteen days after adequate preparation, the patient underwent resection of the retroperitoneal tumor and gastric stromal tumor, which lasted approximately 140 minutes, and 50 ml of blood was lost. Intraoperative blood pressure was stable between 120-130 mmHg/80-90 mmHg. The surgically resected retroperitoneal tumor was solid, not encapsulated, and fuchsia in color and had irregular margins (Figure 1C), while the gastric tumor was solid, completely encapsulated, and whitish in color and had a complete light edge (Figure 1D).

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Then, the retroperitoneal tumor showed abundant blood vessels without obvious capsule and nerve invasion under the microscope. The tumor cells were consistent with each other with a thick beam-like structure, focal acinar-like arrangement, abundant cytoplasm and red staining (Figure 2A). After 2 days, the Immunohistochemistry was positive for CgA, Syn, S-100, GATA-3, and Ki67 (2%) and negative for CK (AE1/AE3), inhibin-a, HMB45, and SDHB (Figure 2C). Spindle cells and epithelioid cells were both observed under the microscope in the gastric stromal tumor, and the mitotic count was less than 1/50 HPF (Figure 2B). Immunohistochemistry was positive for CD117, CD34, nestin, SDHA, desmin, DOG-1, and Ki67 (1%) and negative for S-100 and SDHB (Figure 2D).

Finally, the patient's surgically excised mass was subsequently subjected to DNA sequencing using the Haplox company platform (Shenzhen, China). The data indicated that SDHB gene mutations existed in both the retroperitoneal and gastric tumors. This mutation was a frameshift mutation located in exon 3, which causes the amino acid at position 80 of SDHB to change from lysine to arginine (L80R) and forms a stop codon at position 8 after the mutation, causing gene transcription degradation or the formation of a truncated protein, leading to loss of function of the gene. It is well known that the functional mutation of this gene is a pathogenic mutation [8,9]. This mutation site is a new mutation subtype that has not yet been reported. Histopathological examination and IHC staining of the surgically resected retroperitoneal mass and gastric mass indicated that they were a PGL and a GIST, respectively. Both tumors shared the SDHB gene mutation. DNA sequencing results showed that the SDHB gene exhibited a new mutation site that has not yet been reported. The case was eventually diagnosed as CSS associated with SDHB deficiency due to a new mutation site.

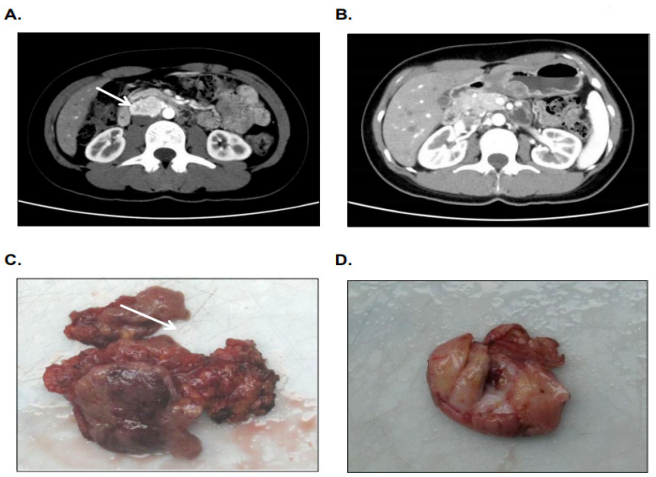

Figure 1: (A): Abdominal contrast-enhanced CT. **(B)**: A 3 cm gastric submucosal tumor. C: The retroperitoneal tumor. D: The gastric tumor was solid, completely encapsulated, and whitish in color and had a completely light edge.

Discussion

The clinical manifestations of CSS are not significant, often only elevated blood pressure and unexpectedly discovered abnormal lumps [10]. The stability of the SDH complex is affected by the loss of expression of any of its subunits, which is usually manifested by the loss of SDHB expression. Therefore, IHC of SDHB has been shown to be a tractable surrogate marker for SDH deficiency [1]. However, it is worth noting that GISTs are usually multifocal and almost always limited to the stomach, with some preference for the gastric antrum and distal stomach. The median size is approximately 5 cm, and the tumor cells

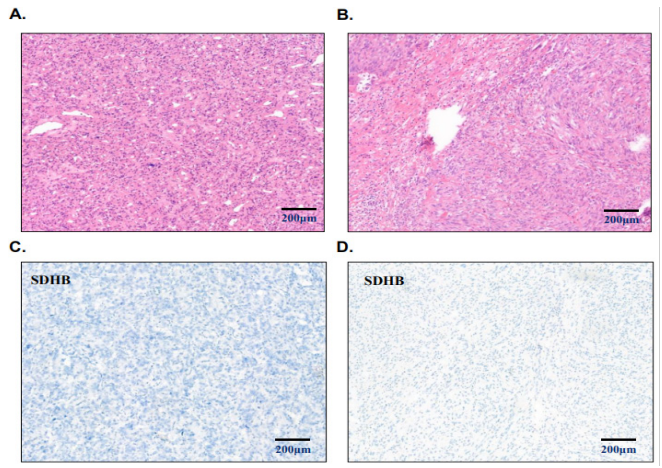

Figure 2: (A): The tumor cells were consistent with each other, forming a thick beam-like structure and focal acinar-like arrangement with abundant cytoplasm and red staining. **(B)**: Spindle cells and epithelioid cells were both observed under the microscope in the gastric stromal tumor, and the mitotic count was less than 1/50 HPF. **(C)**: Immunohistochemistry was positive for CgA, Syn, S-100, GATA-3, and Ki67 (2%) and negative for CK (AE1/AE3), inhibin-a, HMB45, and SDHB. **(D)**: Immunohistochemistry was positive for CD117, CD34, nestin, SDHA, desmin, DOG-1, and Ki67 (1%) and negative for S-100 and SDHB.

show epithelioid cytomorphology and a plexiform pattern of involvement of the muscularis propria [1]. Most patients with GISTs with SDHB deficiency have organ metastasis. The most common sites of metastasis are the liver, peritoneum, lymph nodes and lung tissue [11,12]. Paraganglioma with SDHB mutation also has a higher risk of metastasis than sporadic PGLs [2]. Hence, many studies recommend Magnetic Resonance Imaging (MRI) screening every three to five years for patients with SDHA, SDHC, and SDHD mutations who have indolent tumor growth. For individuals with SDHB mutations, tumors grow rapidly, and the patients should undergo MRI screening every two years [3]. For the treatment of CSS, surgical resection is the first choice, and pharmacological therapies for many SDH-deficient tumors, especially CSS, are still under further investigation [13].

Here, we present a case with a new mutation site in SDHB that has not yet been reported. The patient's clinical symptoms were not specific, and imaging examination provided us with great help in diagnosis and treatment. We provided surgical treatment for the patient, and the postoperative pathological and immunohistochemical results suggested CSS. DNA sequencing to determine SDHB mutations in the patient confirmed the diagnosis of CSS. Genetic testing can provide a definitive diagnosis of CSS. The patient's blood pressure was absolutely controlled after surgery, and reassuringly, her postoperative imaging was tumor-free. Due to the high likelihood of relapse in the patient, we recommend that she should be reviewed regularly and followed long term.

Conclusion

We provide a case of CSS associated with a mutation in the SDHB gene that has not yet been reported. Diagnosis of CSS is difficult, and the clinical manifestations are not specific. Genetic testing is an effective test for the diagnosis of CSS.

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