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LETTER TO THE EDITOR

A rare hereditary and metastatic paraganglioma involved in both spermatic cord and testis

Shuoming Luo[1] · Zhenqi Liu[2] · Zhiguang Zhou[1]

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To the Editor,

Paragangliomas (PGLs) are rare neuroendocrine tumors with a strong genetic background. We herein present a case of functional PGL involving both the testis and spermatic cord with distant metastasis and a germline SDHB mutation.

In October 2016, a 28-year-old Chinese man was admitted to our hospital with a chief complaint of hypertension for 3 years, paroxysmal palpitations, hyperhidrosis, and chest distress for 5 months, and aggravation for 2 h. He was diagnosed with type 1 diabetes 15 years ago based on symptoms of diabetic ketoacidosis at onset. His father had hypertension and diabetes. On admission, his blood pressure was 170/112 mmHg and heart rate was 106 times per minute with symptoms of adrenergic hyperstimulation. Physical examination revealed a palpable, painless, and firm mass in the right inguen. All parameters in comprehensive metabolic panel were normal, including kidney and liver function, blood albumin levels, electrolyte levels, and lipid profiles with normal thyroid function. His diabetes was poorly controlled and his $HbA1_c$ was 11.2% while he was taking 57 units of insulin on a basal/bolus regimen. Fasting C peptide was undetectable and diabetes-related autoantibodies were negative. The levels of 24-h urine vanillylmandelic acid 117.8 umol/day (normal reference range 0.0–68.6) and plasma dopamine 220.69 pg/ml (0.00–600.00), norepinephrine 3333.11 pg/ml (0.00–600.00) were all remarkably elevated. Bilateral adrenal gland computed tomography did not show any abnormality. Subsequent 18-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) revealed multiple, intensely hypermetabolic masses, located in the right testis (tumor size 1.5 × 1.5 × 1.0 cm), right inguen (3.5 × 2.8 × 2.5 cm), right lung (1.0 × 1.0 × 1.0 cm), and retroperitoneum (multiple enlarged lymph nodes), respectively (Fig. 1).

He underwent a successful resection of right testicular and right inguinal tumors and abnormally enlarged retroperitoneal lymph nodes. Right pulmonary mass was resected 2 months later. A diagnosis of testicular and spermatic cord paragangliomas (PGLs) with metastases to the retroperitoneal region and right lung was confirmed by pathologic examination and immunohistochemical analysis. Analysis of PGL-associated genes showed a succinate dehydrogenase complex subunits B (SDHB) mutation with deletion of exon 1. Testing of his parents showed that his father was positive for the same SDHB mutation.

After the initial surgery, all hyperadrenergic symptoms resolved and antihypertensives were discontinued with blood pressure returning back to normal (120/78 mmHg). Plasma catecholamine concentrations were normalized. At his follow-up visit one and half years later, fasting plasma C-peptide levels increased from previous < 5.50 pmol/L to the highest 229.0 pmol/L, and 2-h post-prandial C-peptide levels from 62.4 pmol/L to the highest 555.8 pmol/L. Both daily insulin dosage and $HbA1_c$ prominently decreased. Repeat PET/CT examination showed no tumor residues or recurrence.

PGLs are located anywhere from the base of the skull to the pelvis, but most commonly arise in the abdomen. It may occasionally occur at unusual sites such as urinary bladder and other urogenital tracts. To date, only 10 cases of PGLs in spermatic cord [1], one case in testis [2] and one case in paratestis [3] were documented in the English literatures.

This case raises some important learning points. First, while it is extremely rare for PGLs to present with secondary diabetes mimicking type 1 diabetes, we speculate that his diabetes is possibly secondary to PGLs given the drastic improvement in his pancreatic beta cell function after the surgery. His glycemic control was poor and his insulin requirement was high prior to the surgery. Tumor

✉ Zhiguang Zhou
zhouzhiguang@csu.edu.cn

[1] Department of Metabolism and Endocrinology, the Second Xiangya Hospital, Central South University, Changsha, Hunan 410011, China

[2] Division of Endocrinology and Metabolism, Department of Internal Medicine, University of Virginia Health System, Charlottesville, VA, USA

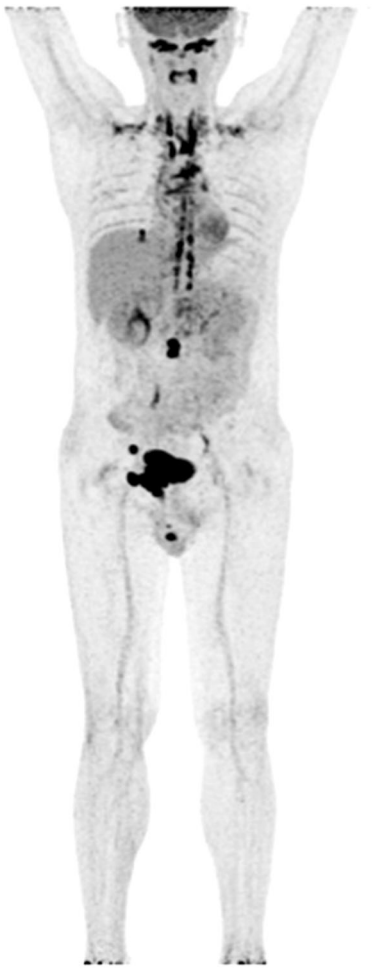

Fig. 1 PET image in coronal projection showing multiple intensely hypermetabolic masses in the right testis, right inguen, retroperitoneum, and right lung, with a SUVmax of 15.5, 24.7, 22.7, and 8.7, respectively. Diffusely increased glucose metabolism shadow representing brown fat were seen at retroperitoneum, mediastinum vicinity, paratracheal vicinity, bilateral scapular regions, and thoracic vertebrae vicinity

resection normalized plasma catecholamines as well as blood pressure, and decreased insulin requirement by ~60% with excellent glycemic control. However, we cannot confirm that his T1D is truly secondary to PGL because of his diabetes for 15 years. Another possibility is he did have type 1 diabetes and excess catecholamines secretion from the PGLs worsened his glycemic control. Approximately 35~50% of patients with pheochromocytomas have glucose intolerance or diabetes but data from patients with PGLs are lacking. The pathophysiology involves inhibition of insulin secretion, stimulation of glucagon secretion, and increases insulin resistance in the periphery due to overproduced catecholamines. The findings alert the clinicians to the probability of functional PGLs in young patients with insulin-requiring diabetes and hypertension.

Second, SDHB mutations have been mostly associated with catecholamine-secreting familial PGLs. The presence of germline SDHB mutation should alert the clinicians the possibility of distant metastasis as it is found in more than 40% of metastatic PGLs [4]. Although his father currently has no evidence of PGLs' hyperadrenergic symptoms, he should be monitored closely as he carries the SDHB mutation and also has hypertension and diabetes. Unfortunately, his father refuses resolutely to carry out any examinations about PGLs because of no money and resistance at present.

The overall 5-year survival rate of metastatic PGLs varies between 34 and 60%. It is of interest to note that he returned back to normal biochemically and became normotensive after the initial surgery, before the resection of pulmonary metastasis. This means the pulmonary metastatic lesions were not functional. Hence, the patient needs long term follow-up, both biochemically and through imaging studies.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent was obtained from the patient and his parents included in the study.

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