Treatment Strategy for Inoperable Von Hippel-Lindau-related Phaeochromocytoma: a case report and literature review

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Abstract

Phaeochromocytomas and paragangliomas (PPGL) are rare neuroendocrine tumors. Some advanced PPGLs are inoperable. Treatment strategies for inoperable PPGLs should be discussed case by case under the coordination of multidisciplinary team. Target organ management is crucial in improving life quality and prognosis.

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Key Clinical Message

Phaeochromocytomas and paragangliomas (PPGL) are rare neuroendocrine tumors. Some advanced PPGLs are inoperable. Treatment strategies for inoperable PPGLs should be discussed case by case under the coordination of multidisciplinary team. Target organ management is crucial in improving life quality and prognosis.

Keywords:

Phaeochromocytoma, von Hippel Lindau disease, Recurrence.

Introduction

Von Hippel-Lindau (VHL) syndrome is a VHL-gene-mutation-related disease with autosomal dominant inheritance. The incidence rate reported abroad is about 1:36000 in the general population.[1] It frequently presents as benign and malignant multiorgan tumors, involving brain, spinal cord, retina, pancreas, kidneys, adrenal glands, epididymis and other structures. Among VHL patients, phaeochromocytomas are diagnosed at the average age of 30 years old, with a metastatic risk of approximately 5%.[2] The primary lesions usually locate in bilateral adrenal glands, and extra-adrenal paraganglioma could occur as the disease progresses. Due to rareness of phaeochromocytoma and paraganglioma (PPGL), clinicians often lack experience to deal with relative cases. Here, we report a case of VHL-related recurrent phaeochromocytoma with multiorgan involvement and review the literature.

Case History

A 47-year-old male patient, complaining paroxysmal palpitation and sweating, was admitted to our hospital in March 25, 2015. According to the medical history provided, he was discovered a left adrenal mass(7×5×4cm large) 6 years earlier. At the onset, there was no remarkable abnormalities except impaired glucose metabolism (fasting blood glucose 11mmol/L, postprandial blood glucose 23mmol/L). An open left adrenal tumor resection was performed in September 11, 2009 after short-term insulin treatment and drug preparation. Postoperative pathological examinations suggested a phaeochromocytoma. The patient's glucose regulation improved after resection without any glucose-lowering medications, remaining only a slight increase in postprandial blood glucose (fasting blood glucose 4-5mmol/L, postprandial blood glucose 9-10mmol/L). However, he underwent a secondary operation in April 8, 2011 due to recurrence in bilateral adrenal glands. In the next year, follow-up CT scan showed several obviously contrast-enhanced nodules in the right adrenal gland, pancreas and near the abdominal aorta, revealing a second recurrence. Regular imaging examinations showed no significant progress and the patient had no overt presentations until the visit to our hospital. On further questioning, the patient admitted a positive family history: his elder son was found phaeochromocytomas in both adrenal glands and received surgical treatment in 2009 (at the age of 18), and the tumors recurred in 2011. No tumors were found in other relatives.

Examinations

No abnormal physical signs were disclosed after admission. Vital signs were stable: HR 81 bpm, BP 96/72 mmHg. Laboratory testing revealed nothing special but a moderate renal impairment: serum creatinine 147 μmol/L. Comprehensive endocrine workup confirmed diabetes. Functions of adrenal cortex, adrenal medulla, thyroid gland, parathyroid gland, and pituitary gland were unremarkable (Table 1).

Magnetic resonance imaging (MRI) result was roughly similar to those previously done in other hospitals. MRI revealed multiple nodules in right adrenal gland, pancreas, and para-aortic area, as well as multiple cysts located in the pancreas and kidneys. Further PET/CT showed catecholamine hypermetabolism in those intra-abdominal nodules. We also discovered a marked left kidney atrophy, which may be a postoperative change. Thyroid ultrasonography and pituitary MRI had nothing unusual.

Outcome and Follow-up

Based on multidisciplinary team discussion, the patient was given phenoxybenzamine 10mg per day to alleviate clinical symptoms. Palpitations and sweating were relieved after initiation of α-adrenoceptor blocker therapy. Blood pressure remained normal and stable. Blood glucose levels were kept in good control by single oral anti-diabetic agent. Besides, the patient was required to have yearly examinations, including endocrine function checkup and MRI scans. Plasma catecholamines, plasma metanephrine and normetanephrine (MNs), and urinary vanillylmandelic acid had maintained in the normal range since 2015. MRI scans revealed a gradual enlargement in the para-aortic nodule (). A new contrast-enhanced lesion in the right kidney was

discovered (Figure 1). Pancreatic cysts decreased in size while renal cysts grew larger. The patient had recurrent phaeochromocytomas and multiorgan cysts, as well as a positive family history, which was highly indicative of VHL disease. With the patient's consent, we underwent a PPGL genetic testing in September 2020, and discovered a heterozygous pathogenic mutation of the VHL gene (NM_000551.3:c.278G¿A). We also focused on target organ management. Electrocardiograph, echocardiogram, renal function and funduscopic examinations were assessed yearly. No cardiac vascular diseases, kidney function decline or retinal alterations were observed. Vascular ultrasound showed arterial atherosclerosis with multiple plaques at the beginning of the observation. Antiplatelet agents (aspirin 100mg per day) and lipid-lowering drug (Lipitor 10mg per day) was given since 2017. The vascular changes were successfully reversed at the last review in 2021.

Discussion

In this paper, we report the case of recurrent phaeochromocytoma in a middle-aged male patient with atypical clinical presentations that could be well controlled with medication. The patient had already received two adrenalectomies before his admission. According to the pathological reports provided, all of the removed tumors underwent immunohistochemistry analysis, and suggested a positive expression of neuroendocrine markers (Syn and CgA). Ki-67 index was no more than 2%, indicating a low proliferation capacity, and was consistent with the slow progression of the disease. Laboratory results did not reveal any endocrine abnormalities. However, there was always a local recurrence following surgery and distant lesions appeared as disease developed. Although we didn't perform a biopsy of extra-adrenal lesions, PET/CT showed catecholamine hypermetabolism in right adrenal gland and several intra-abdominal nodules, indicating the possibility of malignant phaeochromocytoma.

Currently, the World Health Organization (WHO) has replaced the previous concept of 'malignant PPGL' with 'metastatic PPGL', and proposes that all PPGL should have malignant potential.[3] A definite diagnosis of malignancy can only be validated by the presence of metastasis in non-chromaffin tissues (such as brain, lung, liver, bones or lymph nodes). There have already been several methods to predict metastasis of PPGL. Some scoring systems, like PASS and GAPP, are primarily based on histopathological features. Both systems have been proved to be highly sensitive to metastatic potential, but lack specificity.[4, 5] Metastatic and non-metastatic PPGLs are similar histologically and hard to distinguish from each other. It may be more convincing to rule out the possibility of malignancy when scores are low, rather than to make a metastatic prediction with high scores. Analogously, it is also difficult to determine the metastatic potential of PPGL by a single biomarker. Ki-67 is a proliferative marker that has been shown to be predictive of metastases in PPGL. But some studies indicate that Ki-67 index has a low sensitivity, and correlates with progression-free survival rather than the occurrence of metastasis. The recommended thresholds are also disputed. Another system, the COPPS score, integrates clinic-pathological features and immunohistochemical markers (PS100 losses, SDHB immunostaining) for risk assessment of metastasis, and exhibits an excellent reproducibility (AUROC = 0.981).[6] However, in our case, slides of primary tumor were not available and immunohistochemical results were incomplete, which limited the application of COPPS. Taking clinical features into account, the primary tumor was large, and showed a strong tendency to recurrence, but presented no rapid invasion with a biochemical silent phenotype. It might be judged as a slowly progressing metastatic PPGL.

The preferred treatment for metastatic PPGL is tumor resection. Conservative treatments include the following methods. Chemotherapy is mainly used for rapid progressing metastatic PPGL. The common chemotherapy regimen is CVD regimen, a combination of cyclophosphamide, vincristine and dacarbazine. It is reported that the complete remission rate of CVD regimen is 4%, while partial remission rate is 37%, and the rate of stabilization is 14%, as assessed by tumor volume reductions. [7]However, it may cause severe adverse reactions, such as marrow suppression and hypertensive crisis. Nuclide therapy, including metaiodobenzylguanidine (MIBG) therapy and peptide receptor radionuclide therapy (PRRT), needs to evaluate the nuclide uptake in tumor cells before treatment. The conventional MIBG preparations has been shown to prolong survival with an increased 5-year survival rate of 45%-68% and achieve stabilization in 73%-79% of patients. However, the preparations contain large doses of unlabeled MIBG that disrupt the

norepinephrine-reuptake mechanism, leading to very low specific activity and life-threatening side effects. In comparison, high-specific-activity MIBG shows improved efficacy and tolerability in vivo. [8]So far, the new preparations haven't been available domestically. PRRT is considered as a viable alternative to chemotherapy and MIBG therapy. Meta-analyses reported PRRT remission rate and disease control rate of 25% and 84%, respectively. [9]MIBG treatment and PRRT are usually applied to advanced systemic PPGL. Radiofrequency ablation and embolization perform well in local control. Kohlenberg, J et ml. reported an ablative efficacy of 86% local control on imaging, ang 92% symptomatic remission with a low incidence of serious complications.[10] Targeted therapeutic agents, for instance, tyrosine kinase inhibitors, also show potential efficacy, especially in patients bearing SDHB gene mutations. Relevant clinical trials are ongoing and there is still a lot to be done in this area.[11]

In this case, due to multiorgan involvement, and intra-abdominal adhesions caused by previous operations, surgery became risky. We turned to conservative options for a safer solution. Chemotherapy could act on the whole body and was usually used in the treatment of advanced PPGL. However, chemotherapy-induced myelosuppression, and severe infection and intracranial hemorrhage that may occur afterwards, might be fatal. It was not a priority to take the hazard for a slow-progressing PPGL with mild symptoms. Considering the life-threatening side effects of conventional MIBG preparations, MIBG therapy was not preferred as well. Furthermore, targeted therapy was costly and we had to take into account the patient's financial burden. Radiofrequency ablation and embolization might be useful, but were rarely performed in PPGL in our hospital. The efficacy was uncertain. We decided to wait and see under the close observation of the multidisciplinary team.

PPGL is of great heterogeneity, progression and metastasis may occur even 10 years after diagnosis. All PPGL patients need long-term assessment, basically containing endocrine workup and imaging examinations. MRI is preferred to reduce radiation. Genetic testing should be completed early if possible, especially in patients with large primary tumors ([?]5-6cm), extra-adrenal tumors, positive family history, recurrence, or young onset. For cost saving, screening for RET, VHL and SDHx genes may be recommended. Ma, X et ml. reported a genetic profile in Chinese PPGL patients in a single center study: SDHB mutation is the most frequent, accounting for 20%, followed by RET (3.8%), VHL (3.8%), SDHD (2.5%), SDHA (2.2%).[12] Based on genetic results, extra screening should be added. VHL patients have to pay attention to VHL-associated tumors, and receive careful ophthalmic examinations and MRI scans of the head and abdomen. At-risk relatives should also undergo comprehensive screening and molecular genetic testing early. [2]For biochemical silent PPGLs, apart from regular checkup, target organ management is also necessary, to avoid complications. In our case, the patient underwent cardiovascular and renal function screening, glucose level and lipid profile checkup every 12 months. Interestingly, we observed no significant vascular benefits with the use of α-adrenoceptor blocker. Given that the tumors were non-functional, there was a probability that α-adrenoceptor blocker application had a limited effect. Significant improvement occurred after the initiation of overall target organ management.

In conclusion, some advanced phaeochromocytomas and paragangliomas are unresectable. Therapeutic strategies are recommended to be selected under the coordination of a multidisciplinary team according to concrete situations. Watch and wait may become a choice when PPGL is inoperable but slow-progressing. Symptom control and effective management of target organ damage contribute to better clinical outcomes. Long-term benefits still need to be confirmed. As the observation continues, we may learn more.

Authorship

CS: reviewed literature and wrote the manuscript. XL and JC: collected data and prepared the images. YG and SZ: reviewed the manuscript.

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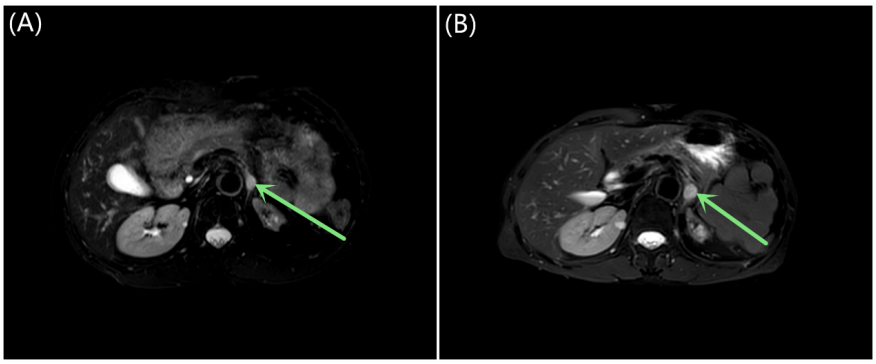
Table 1. Endocrine function workup results in 2015 revealed no remarkable abnormality.

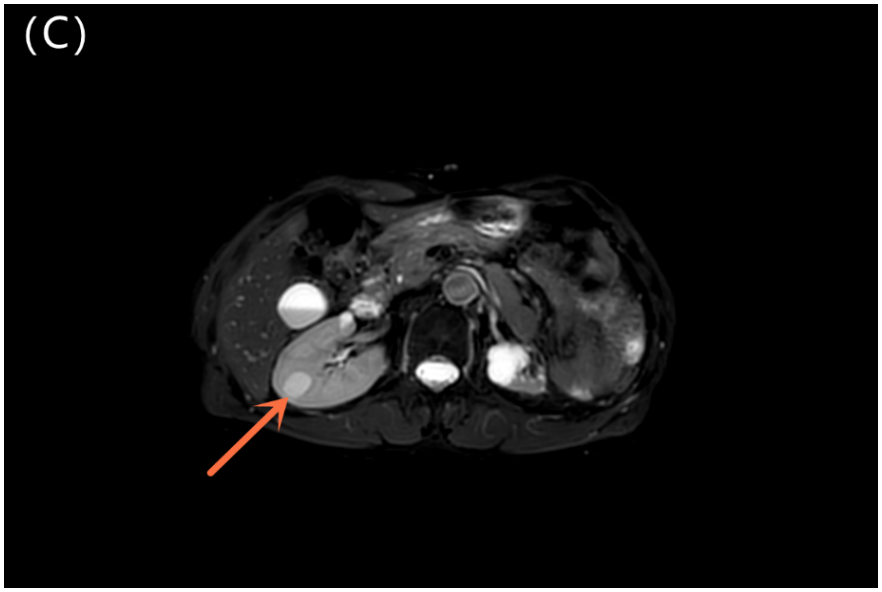
Oral Glucose Tolerance Test

Time, hour	Time, hour	Time, hour
Blood glucose, mmol/L	Blood glucose, mmol/L	Blood glucose, mm
Insulin, mu/L	Insulin, mu/L	Insulin, mu/L
C-peptide, pmol/L	C-peptide, pmol/L	C-peptide, pmol/L
ACTH and Cortisol Rhythm	**ACTH and Cortisol Rhythm**	**ACTH and Cort**
Time	8 am	8 am
ACTH, pg/ml	63	63
Cortisol, nmol/L	497.13	497.13
Salivary Cortisol, nmol/L	/	/
Low-dose Dexamethasone Suppression Test	**Low-dose Dexamethasone Suppression Test**	**Low-dose Dexam**
Cortisol before, nmol/L	Cortisol before, nmol/L	Cortisol before, nm
Cortisol after, nmol/L	Cortisol after, nmol/L	Cortisol after, nmo
Aldosteronism Screening Test	**Aldosteronism Screening Test**	**Aldosteronism S**
Position	Supine	Supine
Aldosterone, ng/L	167.6	167.6

PRA, ng/ml/h	4.4	4.4
ARR ratio	3.81	3.81
PPGL Screening	**PPGL Screening**	**PPGL Screening**
Epinephrine, pg/ml	Epinephrine, pg/ml	14.94
Norepinephrine, pg/ml	Norepinephrine, pg/ml	387.78
Dopamine, pg/ml	Dopamine, pg/ml	40.35
Urinary Hormone Measurement	**Urinary Hormone Measurement**	**Urinary Hormon**
Urinary aldosterone, µg/24h	Urinary aldosterone, µg/24h	Urinary aldosteron
Urinary Cortisol, nmol/24h	Urinary Cortisol, nmol/24h	Urinary Cortisol, n
Urinary VMA, mg/24h	Urinary VMA, mg/24h	Urinary VMA, mg
Thyroid Function	**Thyroid Function**	**Thyroid Functio**
T3, nmol/L	1.35	1.35
FT3, pmol/L	5.22	5.22
TSH, mu/L	0.963	0.963
TG Ab, IU/ml	¡15.0	¡15.0
Parathyroid Function	**Parathyroid Function**	**Parathyroid Fun**
PTH, pg/ml	50	50
Serum Calcium, mmol/L	2.32	2.32
Pituitary Function	**Pituitary Function**	**Pituitary Functi**
Growth Hormone, ng/ml	Growth Hormone, ng/ml	Growth Hormone,

Figure 1.





(A-B) MRI scans in 2015 and 2020 revealed a slow enlargement in the para-aortic nodule (from 11.2×8.3mm to 17.0×11.2mm, green arrow); (C) a new contrast-enhanced nodule in the right kidney (orange arrow) was discovered.