A Rare Coexistence of Pheochromocytoma and Parkinson’s Disease With Diagnostic Challenges : A Case Report

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Abstract:
We herein report a case of pheochromocytoma occurring in the course of Parkinson’s disease. The coexistence of these two disease is extremely rare, with only four cases hitherto reported across the public databases. It is also noteworthy that biochemical tests, which are critical for the diagnosis of pheochromocytoma, are severely confounded by dopaminergic medications for Parkinson’s disease, highlighting the importance of image-based modalities in this setting. We further attempted to gain insight into the potential molecular mechanisms, proposing that hypoxia-inducible factor (HIF) signaling could make these two diseases mutually exclusive, while excessive reactive oxygen species (ROS) could enable their coexistence.

Key words: Pheochromocytoma, Parkinson’s disease, dopaminergic medications, rare coexistence, HIF-ROS

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Introduction

Pheochromocytoma is a neural crest-derived tumor occurring in the medullary adrenal gland chromaffin cells with a prevalence of 0.1% to 0.6% in patients affected by hypertension (1). It is characterized by the enhanced biosynthesis and secretion of catecholamines, causing multiple clinical manifestations, including paroxysmal hypertension, headache, sweating and weight loss. On the other hand, Parkinson’s disease is a neurodegenerative disorder that affects 1%-2% of the population and is characterized by decreased levels of catecholamines, especially dopamine, in the substantia nigra in the midbrain that lead to motor dysfunction as well as other neurological deficits.

Since most Parkinson’s disease treatments aim to restore dopaminergic activity by modulating catecholamine metabolism, biochemical tests to measure catecholamine levels are influenced by those medications (2), making the diagnosis of pheochromocytoma extremely challenging (3). In addition, the coexistence of these two diseases is very rare, and to date, only four cases have been reported. Therefore, these cases might offer a unique opportunity to gain insights into the pathological underpinnings of both diseases (4-7).

Recent advances in understanding the genetics of pheochromocytoma have revealed that approximately 40% of pheochromocytomas carry a germline mutation in one of the 15 genes that have been identified, which include Neurofibromin 1 (NF1), ret proto-oncogene (RET), von Hippel-Lindau tumor suppressor (VHL), succinate dehydrogenase complex subunit A/BC/D (SDHA/B/C/D), transmembrane protein 127 (TMEM127) and MYC-associated factor X (MAX) (8). A genetic analysis of rare patients with both pheochromocytoma and Parkinson’s disease may be useful for revealing the molecular components of the pathologies, although this perspective has not been applied in previously published reports.
Table 1.

| Plasma                                      | results (normal range) |
|---------------------------------------------|------------------------|
| epinephrine (pg/mL)                        | 22.0 <170              |
| norepinephrine (pg/mL)                     | 620 150-570            |
| dopamine (pg/mL)                           | 1,320 <30              |

Biochemical analysis of plasma samples.

Table 2.

| Urine                                      | Day 1       | Day 2       | (normal range) |
|--------------------------------------------|-------------|-------------|----------------|
| epinephrine (µg/day)                       | 68.0        | 15.6        | 1-23           |
| norepinephrine (µg/day)                    | 343.4       | 246         | 29-120         |
| dopamine (µg/day)                          | 78,200      | 55,500      | 100-1,000      |
| metanephrine (mg/day)                      | 0.1         | 0.09        | 0.05-0.20      |
| normetanephrine (mg/day)                   | 0.61        | 0.63        | 0.10-0.28      |

Biochemical analysis of urine samples on two consecutive days.

Case Presentation

A 77-year-old Japanese man who was receiving L-dopa, carbidopa, entacapone and salegiline hydrochloride for the treatment of Parkinson’s disease was brought to a local hospital with thoracic trauma, where a left adrenal mass (20 mm ×17 mm) was incidentally identified on computed tomography (CT). He had a 5-year history of headaches and paroxysmal hypertension up to 200 mmHg. A serum biochemical analysis showed elevated catecholamine levels: dopamine (4,651 pg/ml, normal range <20 pg/mL), norepinephrine (797 pg/mL, normal range 100-450 pg/mL) and epinephrine (27 pg/mL, normal range <100 pg/mL). Based on these findings, he was referred to our hospital for the diagnosis of pheochromocytoma.

His stage of Parkinson’s disease was relatively advanced, showing not only common symptoms of muscle rigidity and tremor but also uncontrollable wearing-off and dyskinesia. Although dopaminergic medications for Parkinson’s disease can cause pseudopheochromocytomas, which are symptoms suggestive of pheochromocytoma in the absence of adrenal pathology (4), the patient had never developed overt hypertension during his 17-year history of Parkinson’s disease with those medications. On admission, his blood pressure was 175/86 mmHg, and his pulse rate was 74 bpm without any hypertensive medications.

Selected biochemical test results are shown in Table 2. The dopamine levels were extremely elevated and norepinephrine levels were marginally elevated, while serum chromogranin A levels were not elevated (4.1 pmol/mL, measured by an EIA kit, Yanahara, Japan, normal range 3.0-8.0 pmol/mL). The predominant elevation of dopamine levels together with the fact that dopamine secreting pheochromocytoma is extremely rare and often asymptomatic (9) suggested that the biochemical tests had been confounded by his dopaminergic medications. Therefore, we fully characterized his adrenal mass with multiple imaging modalities. The adrenal mass had early arterial enhancement with contrast wash out on the portal venous phase images on CT, implicating the existence of cortical adenoma (Fig. 1). In contrast, chemical shift imaging on magnetic resonance imaging (MRI) suggested the absence of intracellular lipids (Fig. 2). In addition, 123I-metaiodobenzylguanidine (123I-MIBG) scintigraphy showed an intense uptake into the adrenal mass as well as a reduced cardiac uptake, consistent with his advanced Parkinson’s disease (Fig. 3).

To verify our diagnosis and obtain further supportive information, we preoperatively screened for germline mutations in genes known to be associated with pheochromocytomas using a targeted gene panel (10). However, we detected no germline mutations in SDHB/C/D, RET, TMEM127, VHL or MAX in this case.

As in the other four cases of this rare coexistence, the imaging-based analysis, especially the 123I-MIBG uptake, strongly supported our diagnosis of pheochromocytoma. Consequently, after preoperative management with doxazosin, he underwent laparoscopic adrenalectomy, with fluctuations in his blood pressure ranging from 90 to 190 mmHg. The adrenal mass was proven to be a pheochromocytoma by a histological analysis of the specimens. His blood pressure is adequately controlled with 2.5 mg amlopidine 6 months after the surgery.

Discussion

Only four cases of pheochromocytomas occurring in Parkinson’s disease patients have been reported, and we herein report another case illustrating the challenges in the diagnostic procedure in this coexistence with a pathogenic perspective.

Since Parkinson’s disease is a neurodegenerative disorder characterized by insufficient dopaminergic activity in the midbrain, pharmacological treatment for Parkinson’s disease has been developed to increase the dopamine levels by modulating the catecholamine metabolism. L-dopa is the metabolic precursor and replenishes central dopamine, while carbidopa, the dopa decarboxylase inhibitor, inhibits the peripheral conversion of L-dopa to dopamine. Notably, dopamine is converted to norepinephrine and epinephrine by two-step sequential enzymatic reactions. The catechol-O-methyltransferase (COMT) inhibitor, represented by entacapone in this case, blocks inactivation of catecholamines by O-methylation. The monoamine oxidase inhibitor (selegiline in this case) blocks the catabolism (oxidative deamination) of catecholamines (2). These medications therefore influence catecholamine levels at multiple levels and compromise the clinical assessment of the endogenous catecholamine metabolism (3). To overcome this issue, another biomarker chromogranin A, has been proposed as a surrogate marker with 91% sensitivity (4, 11), although this readout was not elevated in our case. Based on the serum profile
with markedly elevated dopamine levels, pheochromocytomas exclusively secreting dopamine, which are known to be rare, also need to be considered. However, the patient’s serum dopamine levels remained highly elevated even after surgical resection while on medication for Parkinson’s disease, which argues against this possibility. We did not measure the levels of homovanillic acid or vanillylmandelic acid, which are the final metabolites of dopamine and epinephrine/norepinephrine, respectively. It would be interesting to measure these metabolite levels in order to further clarify the strong shift toward dopamine metabolism in this case.

The diagnosis of pheochromocytoma relies mainly on two sets of examinations: a biochemical analysis and an imaging-based analysis. Therefore, when the biochemical
Pheochromocytomas are classified into two clusters depending on the molecular signatures associated with the driver mutations: pseudohypoxia-related tumors (cluster 1 represented by VHL, SDH and HIF2A mutations) and kinase-driven tumors (cluster 2 represented by RET, NF1, TMEM127 and MAX) (8). It is quite straightforward to see a link between cluster 1 and HIF activation. Intriguingly, cluster 2 gene mutations are also known to eventually activate HIF through multiple signaling pathways, including mTORC1 and MYC, suggesting that the known pheochromocytoma mutations lead to HIF activation, irrespective of the clusters (8).

In contrast to this, mounting evidence suggests that HIF1α activation protects against neurodegenerative diseases, including Parkinson’s disease, Alzheimer’s disease, and Huntington’s disease, and dysfunction of genes involved in monogenic Parkinson’s disease may potentially inactivate HIF signaling (15). The activation state of HIF may counterbalance between a predisposition toward pheochromocytoma and that toward Parkinson’s disease, which could plausibly explain why this coexistence is extremely rare (Fig. 4). This hypothesis fits well with the fact that we could not identify any known germline mutations responsible for pheochromocytoma formation in our patient. The known germline mutations would protect against Parkinson’s disease by activating the HIF signaling pathway, suggesting the involvement of an as-yet-unidentified mechanism in this rare coexistence. In agreement with our hypothesis, we observed a markedly diminished immunoreactivity for HIF1α in our case, while that in another representative pheochromocytoma without Parkinson’s disease was robustly strong (Fig. 5), although larger sample sizes will be required to reach a convincing conclusion. Despite the mutually exclusive relationship between pheochromocytoma and Parkinson’s disease, we observed no noticeable changes in the progression of the patient’s Parkinson’s disease before the occurrence and after the surgical resection of the pheochromocytoma, possibly due at least in part to the fact that his Parkinson’s disease was advanced while his pheochromocytoma was relatively small.

Assuming that HIF signaling makes this coexistence rare, there must be some other molecular machinery enabling the coexistence. To gain some insight, we next attempted to decipher the genetic molecular network of these two diseases. We initially analyzed the genes associated with these two diseases (8, 16) using an unbiased gene ontology (GO) analysis, Database for Annotation Visualization and Integrated Discovery (DAVID), which extracted mitochondria as the most critical cellular component commonly associated with these two diseases (Fig. 6). Our literature survey also supported this finding: Ablation of RET was reported to cause mitochondrial deficit, resulting in dopaminergic neurodegeneration by exhibiting crosstalk with parkin (17), while gain-of-function of RET leads to pheochromocytoma. SDH is a critical component of the mitochondrial electron transport chain complex II. Components of the PTEN-induced putative kinase 1 (PINK1)-parkin pathway, which are relatively common monogenic risk genes in Parkinson’s disease, are also critical determinants of mitochondrial processes such as fission and fusion (18). Another key player in the pathogenesis of Parkinson’s disease, α-synuclein, is also localized at the mitochondria (19). NF1 was also reported to inhibit the production of reactive oxygen species (ROS) by modulating the mitochondrial function (20). Excessive ROS production, a hallmark of mitochondrial dysfunction, has been reported to play a causative role in at least some populations of both pheochromocytomas and Parkinson’s disease (21-23). ROS and mitochondrial dysfunction, which are closely interconnected, may be a plausible mechanism enabling this coexistence (Fig. 4). In our patient, there might
Figure 4. A schematic representation of the hypothesized molecular mechanism. Neural crest-derived cells are prone to pheochromocytoma and less prone to Parkinson’s disease with activated HIF. Excessive ROS coupled with mitochondrial dysfunction may play a causative role in both of these diseases.

Figure 5. An immunohistochemical analysis of HIF1α. Sections of pheochromocytomas from our case (A) and another representative case without Parkinson’s disease (B) were stained using anti-HIF1α antibody (Gene Tex, GT10211, 1: 200). Scale bars indicate 50 μm. Upper panels show representative images at higher magnification.
Figure 6. A gene ontology (GO) analysis of genes known to be associated with pheochromocytoma and Parkinson’s disease using the functional annotation tool DAVID. GO terms with p-value <0.01 in a cellular component analysis are shown.

have been molecular events generating excessive ROS while leaving the HIF signaling pathway unaltered by either unknown germline mutations or non-genomic mechanisms which need to be elucidated in a future study.

Conclusion

We described the fifth case of pheochromocytoma occurring in a patient with Parkinson’s disease. Dopaminergic medications for Parkinson’s disease confound biochemical tests for the diagnosis of pheochromocytomas. MIBG scintigraphy was the most useful among the imaging modalities, which is consistent with the four cases published previously. HIF activation may predispose cells towards pheochromocytomas and make the coexistence with Parkinson’s disease rare. Excess ROS coupled with mitochondrial dysfunction may play a causative role in this rare coexistence. Such a coexistence offers valuable opportunities to gain insight into the pathogenesis of both diseases in order to develop more sophisticated diagnostic procedures and therapy.

The authors state that they have no Conflict of Interest (COI).

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Disclosure

The authors declare that they have no competing interests. Written informed consent was obtained from the patient for publication of this case report.

Ethics approval and consent to participate

This report is in accordance with the principles of the Ethics Committee University of Tsukuba Hospital.

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