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【 EDITORIAL 】

Pheochromocytoma and Paraganglioma: Challenges and Opportunities in 2021

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Pheochromocytoma and paraganglioma (PPGL) are rare neuroendocrine tumors that originate from the adrenal and extra-adrenal neural crest-derived paraganglia (1). Catecholamine-secreting PPGL, pheochromocytoma and sympathetic paraganglioma, require a timely diagnosis because they can cause acute hemodynamic instability and life-threatening events (2). If undiagnosed, fatal outcomes may ensue. However, the early diagnosis may be challenging because their clinical presentations are diverse. Classic symptoms include headache, palpitation, sweating, and hypertension and are seen in less than 25% of patients (1). Other symptoms are non-specific, mimicking many other diseases, such as anxiety, tremor, pallor, weight loss, a fever, fatigue, orthostatic hypotension, nausea, and constipation.

The article by Funazaki et al. (3) reported a patient with severe constipation and pseudo intestinal obstruction caused by metastatic paraganglioma. They showed that continuous infusion of the non-selective α-blocker, phentolamine, and subsequent chemotherapy relieved it. It is important to note that both therapies can attenuate the action of excessive catecholamines. Other treatment options include metyrosine, an inhibitor of catecholamine biosynthesis, and, when possible, debulking surgery (4, 5). A retrospective analysis of 396 patients with PPGL revealed that 6% of patients had constipation associated with excessive noradrenaline and classic symptoms (5). The majority had non-metastatic PPGL larger than 5 cm or PPGL with extensive metastases. Early intervention may prevent serious complications, as the combination of fiber, water, and laxatives relieved constipation symptoms.

PPGL poses many challenges for clinicians. First, with the widespread use of computed tomography, they frequently present as asymptomatic incidentalomas. Similar lesions are detected during surveillance of carriers with hereditary PPGL. It is challenging to balance when and how to treat these early lesions of hereditary PPGL. Second, evidence-based medicine challenges conventional PPGL guidelines based on observational studies and expert opinions. For example, the time-honored approach of preoperative adrenergic blockade has been contested (6). Third and most importantly, PPGL is the most strongly hereditary of all tumors (7). More than 20 susceptibility genes have been identified in recent decades, and at least 30-40% of patients have germline mutations (8, 9). This genetic understanding has opened a new avenue to diagnosing and managing PPGL, offering a personalized preemptive approach for both patients and their relatives according to their genetic background. However, in Japan, genetic testing for PPGL is currently not covered by health insurance, except for *RET* in those with medullary thyroid carcinoma. By contrast, this is recommended and covered by health insurance for all patients with PPGL in some countries even when they look sporadic because hereditary PPGL may give no obvious clues on its heredity (8). In this regard, recent progress in cancer genomics with next-generation sequencing technology has highlighted 10 genes predisposing individuals to PPGL: *RET, VHL, SDHA, SDHB, SDHC, SDHD, SDHAF2, MAX, TMEM127,* and *NF1*. These are on the minimal list of clinically actionable gene variants in cancer genetic testing at home and abroad (10, 11). This redefined hereditary PPGL as an "actionable disease." In other words, oncologists who ordered a cancer genetic testing may need to return an unexpected secondary finding of the test, i.e., a pathogenic variant in the above-mentioned genes, to a patient with cancer other than PPGL since this information is deemed clinically useful to better manage hereditary PPGL in the patient's entire family.

Taken together, the above-mentioned challenges underscore the need for a more comprehensive and cooperative approach to be taken by all clinicians and organizations. This is a unique opportunity to provide better care for patients with PPGL, their relatives, and their families.

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