Pheochromocytoma: Progress and Challenges

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Pheochromocytoma is a rare cause of hypertension but is often sought in the workup of secondary hypertension in appropriate subjects, since such a diagnosis provides an opportunity to offer definitive treatment for a disease that is otherwise incurable in most cases and involves chronic use of multiple medications.

Despite progress over the last decade in our ability to detect, localize and treat pheochromocytoma, the most important aspect remains the initial clinical suspicion. In their report in this issue of *IMAJ*, Zeitlin et al. [1] present the case of a malignant paraganglioma of the bladder in a patient with a 12-year history of hypertension and a few incidents of life-threatening hypertensive crises. Once the patient was under their care, the clinical suspicion of pheochromocytoma was raised and a series of biochemical and imaging procedures followed which confirmed the diagnosis.

The typical triad of severe headache, palpitations and diaphoresis accompanying episodes of high blood pressure should lead one to suspect pheochromocytoma. Nevertheless, most subjects with this combination do not have a pheochromocytoma. Several clinical conditions can mimic pheochromocytoma; the most typical mimicking condition is pseudopheochromocytoma [2]. This condition is related to increased adrenoceptor sensitivity rather than increased circulating catecholamines. Therefore, the most important first step is to rule out pheochromocytoma.

Over the last decade data have accumulated with regard to the role of free plasma metanephrines as a screening test for this condition [3,4]. This test has essentially 100% sensitivity in symptomatic patients, which means an ideal negative predictive value and no further workup is needed after a single blood test. In centers where this test is not available, repeated (twice) normal 24-hour urinary collections for both metanephrines and catecholamines have a 95% negative predictive value. Other biochemical tests such as urinary VMA (vanillylmandelic acid) have low sensitivity and should be abandoned since they have no role in the decision-making process.

It is important to note that plasma metanephrines can be relied on only if determined by HPLC (high-performance liquid chromatography) or LCMS (liquid chromotography-mass spectrometry). All other commercially available kits for plasma metanephrines do not have sufficient sensitivity for the purpose of ruling out pheochromocytoma definitively because of detection of conjugated as well as free metanephrines.

Positive results of the screening tests are followed by confirmatory tests. Until recently clonidine suppression and glucagon stimulation tests were used [5]. Glucagon exerts a specific effect on pheochroocytoma cells and not normal chromafin cells [6]. However, in a study of 64 subjects, half with pheochromocytoma, we found that it adds very little to the clonidine suppression test; on the other hand, injecting glucagon can elicit a severe increase in blood pressure [7]. Therefore, the glucagon test should also be abandoned for confirming the diagnosis of pheochromocytoma, but the clonidine suppression test can be used.

With regard to localization, Zeitlin et al. [1] listed the various options of imaging studies. One must ensure that if a CAT scan is ordered for the localization of a tumor the request should specifically note "fat suppressed." This allows the radiologist to provide the maximum information from the imaging study. To look for primary tumors and metastases ^{123}I-MIBG scanning is indicated. A negative scan does not exclude pheochromocytoma, however. The authors mention ^{18}F-dopamine positron emission tomography scanning, but this is currently available only at the U.S. National Institutes of Health and is a research test. An alternative is ^{18}FDG PET scanning, which together with positive biochemical results make the diagnosis of pheochromocytoma very likely and can serve as a means to exclude the presence of metastases when surgery is considered.

In the case presented here the pathological diagnosis was paraganglioma. Paraganglioma shares many features with pheohromocytoma, both clinically and pathogenetically. It is indeed a neuroendocrine tumor arising from the sympathetic nervous system, but unlike pheochromocytoma its cells are negative for chromaffin. It is usually found in the neck, most commonly from the carotid body, and only in rare reported cases was paraganglioma found in other sites, such as in the mediastinum and abdominal cavity. Paraganglioma of the urinary bladder is extremely rare. Malignant paraganglioma is also rare. Malignant paragan-

^{18}FDG-PET = fluorodeoxyglucose-positron emission tomography

glioma of the bladder is therefore exceedingly rare, and the diagnosis was made solely because of clinical suspicion and the appropriate workup by Drs. Zeitlin and colleagues.

Future studies are now directed at exploring the molecular basis of the various forms of pheochromocytoma. We hope that this new avenue will lead to the development of better strategies to detect and treat malignant pheochromocytoma where we often fail, as this challenging case demonstrates.

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