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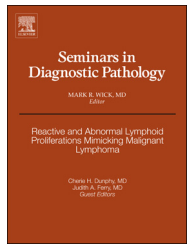

Paragangliomas: Update on differential diagnostic considerations, composite tumors, and recent genetic developments

Thomas G. Papathomas[a,*], *Ronald R. de Krijger*[a], *Arthur S. Tischler*[b]

[a]*Department of Pathology, Josephine Nefkens Institute, Erasmus MC–University Medical Center, P.O. Box 2040, 3000 CA, Rotterdam, The Netherlands*

[b]*Department of Pathology, Tufts Medical Center, Tufts University School of Medicine, Boston, Massachusetts*

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ABSTRACT

Recent developments in molecular genetics have expanded the spectrum of disorders associated with pheochromocytomas (PCCs) and extra-adrenal paragangliomas (PGLs) and have increased the roles of pathologists in helping to guide patient care. At least 30% of these tumors are now known to be hereditary, and germline mutations of at least 10 genes are known to cause the tumors to develop. Genotype–phenotype correlations have been identified, including differences in tumor distribution, catecholamine production, and risk of metastasis, and types of tumors not previously associated with PCC/PGL are now considered in the spectrum of hereditary disease. Important new findings are that mutations of succinate dehydrogenase genes *SDHA*, *SDHB*, *SDHC*, *SDHD*, and *SDHAF2* (collectively "*SDHx*") are responsible for a large percentage of hereditary PCC/PGL and that *SDHB* mutations are strongly correlated with extra-adrenal tumor location, metastasis, and poor prognosis. Further, gastrointestinal stromal tumors and renal tumors are now associated with *SDHx* mutations. A PCC or PGL caused by any of the hereditary susceptibility genes can present as a solitary, apparently sporadic, tumor, and substantial numbers of patients presenting with apparently sporadic tumors harbor occult germline mutations of susceptibility genes. Current roles of pathologists are differential diagnosis of primary tumors and metastases, identification of clues to occult hereditary disease, and triaging of patients for optimal genetic testing by immunohistochemical staining of tumor tissue for the loss of SDHB and SDHA protein. Diagnostic pitfalls are posed by morphological variants of PCC/PGL, unusual anatomic sites of occurrence, and coexisting neuroendocrine tumors of other types in some hereditary syndromes. These pitfalls can be avoided by judicious use of appropriate immunohistochemical stains. Aside from loss of staining for SDHB, criteria for predicting risk of metastasis are still controversial, and "malignancy" is diagnosed only after metastases have occurred. All PCCs/PGLs are considered to pose some risk of metastasis, and long-term follow-up is advised.

* *Corresponding author.*
E-mail address: t.papathomas@erasmusmc.nl (T.G. Papathomas).

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Introduction

Paragangliomas (PGLs) are tumors arising from paraganglia that are normally distributed along supradiaphragmatic (parasympathetic) nerves in the head, neck, and mediastinum; the pre- and paravertebral sympathetic chains; or sympathetic nerve fibers innervating the pelvic and retroperitoneal organs.[1] They are also occasionally reported outside the usual distribution of sympathetic and parasympathetic paraganglia.[2] A pheochromocytoma (PCC) is an intra-adrenal sympathetic PGL with several distinctive characteristics.[3] All PGLs are derived from chromaffin cells or closely related cells of neural crest origin.

This review presents recent developments in PGLs with regard to genetics, diagnostics, and determination of malignancy. In particular, we focus on morphological variants of extra-adrenal PGLs, unusual anatomic sites of occurrence, composite PGLs/PCCs, and potential immunohistochemical pitfalls with the hope that both endocrine and surgical histopathologists can be aware of the broad differential diagnostic spectrum, which may be site-dependent. In addition, we discuss the hereditary susceptibility disorders that are currently known to be associated with the development of PGLs/PCCs, emphasizing genotype–phenotype correlations in familial PGL syndromes and the role of immunohistochemistry (IHC) as a supplementary approach in molecular genetic testing for PGLs and PCCs.

Recent advances in the genetics of paragangliomas

Recent advances in genetics, gene expression profiling, and cell biology have led to enormous progress in our understanding of PCC and PGL pathobiology. Given the fact that germline mutations of at least 10 different genes may account for approximately 30–35% of PCC/PGL cases, these tumors could be regarded as a genetic disease.[2] Further, although somatic mutations of the same susceptibility genes have until recently been considered uncommon causes of sporadic PCC/PGL, Burnichon et al.[4] have now provided evidence suggesting that *NF1* loss of function is a frequent event in the genesis of sporadic tumors. The latter has been reinforced by Welander et al.,[5] who found that the *NF1* gene is the most frequent target of somatic mutations in sporadic PCCs. This may be of particular interest given the fact that *NF1*-associated PCCs share several distinctive features with sporadic PCCs.[6]

The following list encompasses all currently known PCC/PGL susceptibility genes: *RET*, *VHL*, *NF1*, *SDHA*, *SDHB*, *SDHC*, *SDHD*, *SDHAF2*, *FP/TMEM127*, *KIF1Bbeta*, *PHD2/EGLN1*, *MAX*, and *EPAS1/HIF2A*.[7–9] Germline loss-of-function mutations of *SDHA*, *SDHB*, *SDHC*, *SDHD*, *SDHAF2*, and *PHD2/EGLN1* genes along with mutations affecting the *RET* proto-oncogene and *VHL* and *NF1* tumor suppressor genes have been documented to predispose to the development of both PCCs and extra-adrenal PGLs, with tumor location highly dependent on the specific predisposing gene.[2,10–13] It has been shown that germline mutations of *TMEM127* and *MAX* confer risks of extra-adrenal PGLs in addition to PCC.[14,15] In very recent reports, the potential predisposition spectrum of inactivating germline BRCA1-associated protein-1 (*BAP1*) mutations has been extended to PGL,[16] and novel somatic gain-of-function *HIF2A* mutations have been identified in PCC/PGL patients with or without polycythemia.[9,17–22]

Hereditary susceptibility disorders that are well known to be associated with the development of PGLs are multiple endocrine neoplasia type 2 (MEN2), von Hippel–Lindau (VHL) disease, von Recklinghausen neurofibromatosis type 1 (NF1), familial PGL syndromes (PGL 1–4), PGL type 5, Carney–Stratakis dyad, and a newly proposed syndrome of PGL and somatostatinoma associated with polycythemia (Table 1).[7,12,18,31] Carney triad, a syndrome of tumors affecting at least five organs [*stomach*: gastrointestinal stromal tumor (GIST); *lung*: chondroma; *paraganglia*: paraganglioma; *adrenal gland*: adrenocortical adenoma and PCC; and *esophagus*: leiomyoma] is a disorder that still has no established etiology.[28,32] Carney triad is not caused by inactivating mutations of *SDHx* or by activating mutations of *KIT* or *PDGFRA*. Nevertheless, it is generally accepted to be a genetic disorder, possibly caused by somatic mosaicism.[28,33] It is of interest that GIST, specifically epithelioid gastric GIST in most cases, is a component of both the dyad and the triad. GIST is usually the presenting tumor in Carney triad, whereas PGL is the presenting tumor in Carney–Stratakis dyad (PGL and GIST being the legitimate constituents of this autosomal dominant syndrome.[28] Further, GISTs display SDHB immunonegativity in both Carney–Stratakis dyad and Carney triad despite the absence of *SDHx* mutations in the latter.[32] It has therefore been recommended that Carney–Stratakis syndrome or Carney triad be considered in patients who have GISTS that are immunonegative for SDHB, and that testing for germline *SDHx* mutations be considered in all patients, especially younger individuals, with GISTs that are wild type for PDGFR and KIT.[32,34,35] Germline *SDHB* mutation is also associated with a type of renal cell carcinoma that can be recognized by SDHB immunonegativity, thus overlapping the VHL disease spectrum.[36]

Well-documented genotypic–phenotypic correlations exist for tumors in each of the familial PGL syndromes with respect to distribution (Table 1), function, and malignancy. By analyzing a large cohort of previously published carriers of *SDHB*, *SDHC*, and *SDHD* deleterious mutations, Pasini and Stratakis[30] demonstrated the following:

(1) Approximately one-third of affected *SDHB* mutation carriers have a positive family history, which is low in comparison to *SDHD* (61%) and *SDHC* (62.5%).
(2) Median age at diagnosis of the first tumor is higher in SDHC mutation carriers (38 years) than in patients with *SDHB* (32 years) and *SDHD* (33 years) mutations.
(3) Multiple tumors represent a frequent manifestation in *SDHD* mutation carriers (79%) in contrast to patients with *SDHB* and *SDHC* mutations presenting with single tumors in 67% and 73% of cases, respectively.
(4) *SDHD*-affected carriers present more frequently with head and neck PGL only (78%), single or multiple, while PCC (8%) and/or extra-adrenal PGL (1%) are rarely the sole manifestations.
(5) *SDHC*-affected carriers usually present with head and neck PGLs alone (87%), while PCC (3.3%) and/or abdominal PGL (10%) represent rare occurrences.