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Paragangliomas of the Head and Neck: An Overview from Diagnosis to Genetics

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Abstract Paragangliomas (PGL) develop from the parasympathetic system in the head and neck (HN) and arise primarily in four distinct areas: Carotid body, vagal, middle ear, and larynx. Globally, the diagnosis and morphologic features are the same regardless of anatomic site, however the incidence, frequency of genetic alterations/syndromes and differential diagnosis vary. It is now recognized that nearly 40% of all HN PGLs are hereditary, including a significant subset without a known family history. Now pathologists are central to the evaluation for diagnosis and further management of patients with HNPGLs. Specifically, SDHB immunohistochemical evaluation is an excellent screening tool to detect tumors with alterations in the SDH family of genes that represent the majority of hereditary cases in HNPGL. Similarly, SDHB immunohistochemical analysis allows for screening of PGL syndrome associated tumors (gastrointestinal stromal tumor (GIST), renal cell carcinoma (RCC), and pituitary adenomas) that have now been linked by their overlapping gene alterations. Awareness of the spectrum of these syndromes, and their associated tumors, positions the pathologist to augment patient care and surveillance.

Keywords Paraganglioma · SDHB · SDHD · Zellballen · Carotid body tumour · Paraganglioma syndromes

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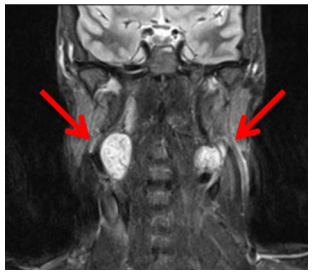
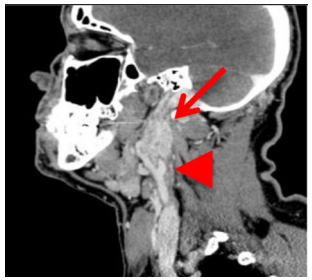
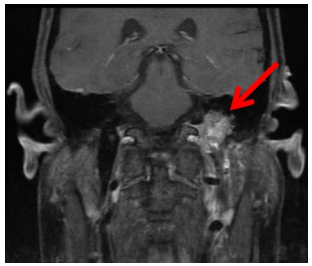
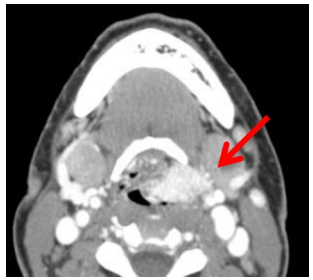
Introduction

The prototypic head and neck (HN) paraganglioma (PGL) is the carotid body tumor where 60% of these tumors occur. The biologic function of the carotid body was deduced to be a chemoreceptor and hence contributed to various name changes for PGLs over the years including: chemodectoma, non-chromaffin PGL, and glomus tumor (unrelated to soft tissue tumors and glomangiomas). It has long been recognized that chronic hypoxia is a risk factor for PGL including those who lived at high altitude, with increased risk particularly in women [1, 2]. Interestingly, this link is now explained by the discovery of over 19 genes predominantly in pseudohypoxia related pathways including over 10 of these genes identified in HNPGLs [3]. The predominant pathway in HNPGL is in the succinate dehydrogenase (SDH) enzyme, which is a multiprotein complex composed of SDHA, SDHB, SDHC, and SDHD proteins in addition to SDHAF2 (a flavination/assembly factor). Succinate dehydrogenase is a critical component between the Krebs cycle and electron transport chain in the mitochondria for which loss of SDH results in ATP production through glycolysis, an inferior/less efficient process [3, 4]. Additionally, these altered pathways enable the tumor cells to grow even in a low oxygen environment [4]. Therefore, alterations in any of the five subunits will result in SDH-deficient tumors, which are each defined by a PGL syndrome 1–5 (described below). With these discoveries, PGLs now represent the most common hereditary condition known with 30–40% of PGLs including those arising in the HN region being familial [5–7].

Table 1 Clinical and pathologic features of head and neck paragangliomas by anatomic site

	Carotid body PGL	Vagal PGL	Middle ear PGL	Laryngeal PGL
Imaging of PGL				
Arising from paraganglia	Carotid body	Along the vagal nerve & nodose ganglion	Adventitia of jugular bulb or along the middle ear medial promontory wall	Superior/supraglottic (80%) & Inferior paired paraganglion
% of HNPGL	**60%**	**10%**	**30%**	**Very rare**
Age decade (mean)	5th–6th[a]	5th	6th[a]	4th–6th (wide age range)
Female: Male	2:1 with 8:1 (high altitudes)	2:1–8:1	3:1–9:1	3:1
Clinical symptoms[b]	Asymptomatic; neck mass near angle of jaw	70% asymptomatic, high neck mass, cranial nerve palsies IX, XI, and/or XIII from compression; <4% clinically functional	Pulsatile tinnitus; hearing loss; aural fullness	Dyspnea; hoarseness; stridor; Vast majority are non-functional *Exclude (atypical) carcinoid if + catecholamine symptoms
Bilateral/multifocal[c]	10–25%	20–40%	Yes often with carotid body +/- vagal PGLs	Rare
Metastatic risk	4–6%	16% [d]	2%	2%
% hereditary	At least 1/3rd	At least 1/3rd	~1/3 [31]	Limited information
Molecular alterations/ PGL Syndromes (see Table 2)	SDHD (50–80%) [31, 49], SDHB (6–35%) [31, 49]; SDHC; SDHAF2 (6%) [49]; TMEM127 [41], VHL (6%) [49]	SDHD (90%) [50]; SDHB (8%) [50]; SDHC (1%) [50]; Rare SDHAF2	PGL syndromes & Neurofibromatosis NF1 (NF1 mutations may also be sporadic)	SDH family (limited information)

Red arrows highlight PGL in each imaging site; Arrowhead in vagal PGL notes sparing of the carotid bifurcation which would occur with carotid body PGL; *CN* cranial nerve; *PGL* paraganglioma; The % of HNPGL is given bold to highlight the variability in incidence of these tumors by site

[a]Malignant cases are often a decade younger at presentation

[b]PGLs arise from the parasympathetic system, are typically non-secretory no catecholamine production (no high blood pressure; tachycardia)

[c]Multifocality/bilateral tumors is associated with hereditary syndromes in the majority of cases

[d]Metastasis versus second primary (multifocal) tumors was not always clarified

Clinical Characteristics

PGLs arise from the paraganglia of the parasympathetic system in the HN and are rarely functional (<1%) with catecholamine production [8, 9]. This highlights a notable distinction from the sympathetically derived (functional) pheochromocytomas (PHEO) of the adrenal gland and extra-adrenal PGL in the abdomen that often present with hypertension and tachycardia. The clinical characteristics for PGL in each of the HN sites (Carotid body, Vagal, Middle ear and Larynx) are detailed in Table 1 showing similarity in age of onset (5th–6th decade) and a female predominance across all four sites. The age of onset though has been noted to be quite broad overall, with hereditary PGL presenting ~ a decade earlier than sporadic tumors, though presentation in childhood is rare. Bilateral/multifocality is common in ~1/4th of cases which is most often hereditary in nature and most commonly associated with SDHD mutations (as described below) [5, 10–13].

Clinical presentation for HNPGLs is often an asymptomatic neck mass for carotid body and vagal PGLs with carotid body tumors being near the angle of the jaw and vagal PGL presenting higher in the neck or as a parapharyngeal mass leading to tonsillar bulging on oral examination. This is in contrast to PGL of the middle ear for which patients present with pulsatile tinnitus or hearing loss [14]. Laryngeal PGL are also symptomatic causing shortness of breath, hoarseness and stridor, which bring these rare tumors to clinical evaluation.

HNPGLs are most commonly encountered, 60% of the time, at the bifurcation of the carotid specifically involving the carotid body. Middle ear PGLs (previously termed jugulotympanic PGLs) represent almost 1/3rd of cases and Vagal PGL occur 10% of the time [14, 15]. Laryngeal PGLs are quite rare with <100 verified cases in the literature to date and further detailed below [16]. There are 2 sets of paraganglia in the larynx by which 80% of laryngeal PGL occur from the superior set in the supraglottic/false cord region [16].

Histopathologic Features

Works by Dr. Barnes and others meticulously define characteristics encountered in HNPGL [13, 14, 16].

The gross resection specimen is often ovoid or fusiform in shape with a firm to rubbery consistency. A variegated cut surface may be present particularly post embolization which is performed secondary to high vascularity in these tumors. The most notable histologic pattern is a nested alveolar or zellballen growth pattern that is helpful but not specific for diagnosing PGLs. Reticulin will highlight the fibrovascular stromal nested pattern. The zellballen nests vary in size from a few to numerous chief cells (Fig. 1a). PGL chief cells range from amphophilic to pink and are

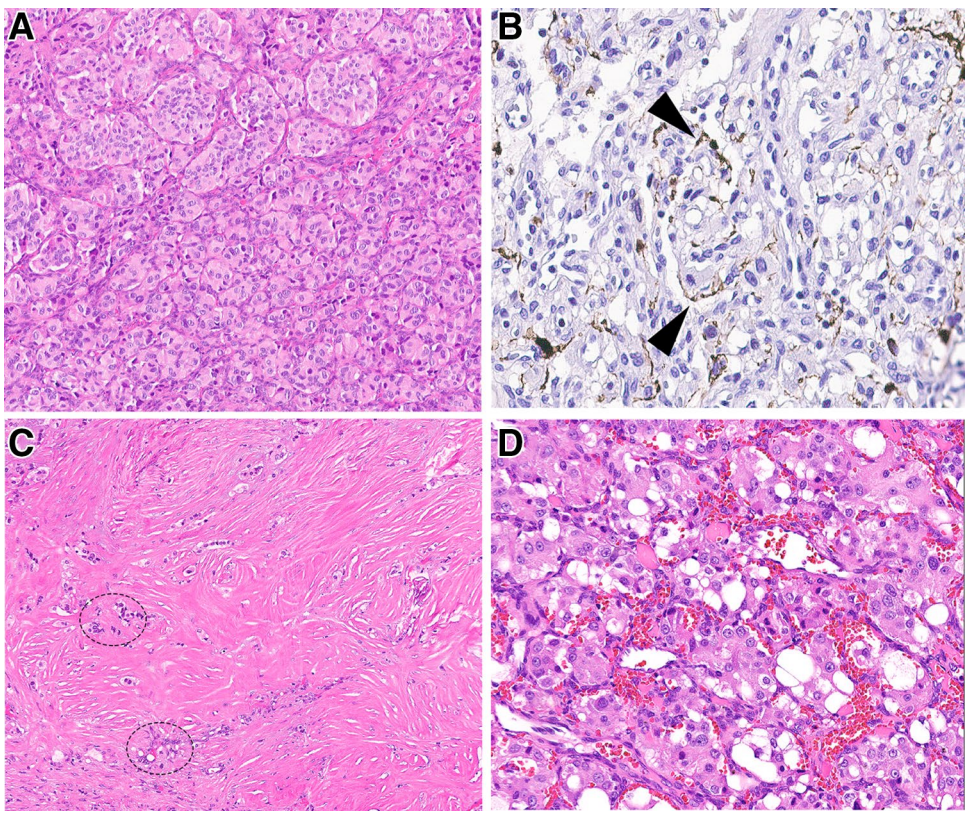


Fig. 1 Paragangliomas are characterized by chief cells forming variable size clusters 'zellballen' (H&E, 200x) (**a**); Supporting sustentacular cells surrounding the zellballen structures are highlighted by S100 (400x) (**b**); The sclerosing variant of paraganglioma shows rare clusters of paraganglioma cells (within dotted circles) in dense collagenous background (H&E 200x) (**c**); Paraganglioma cells may also show vacuolization/clear cell change (H&E 400X) (**d**)

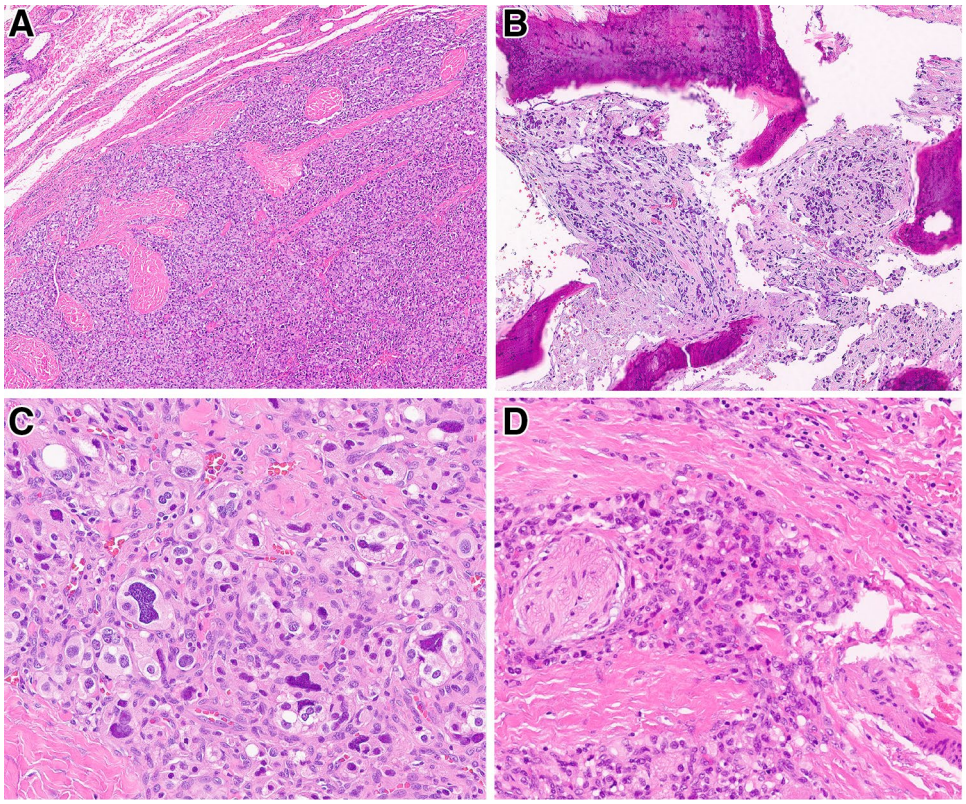


Fig. 2 Histologic features in paraganglioma do not predict behavior (H&E 200x): **a** tumor irregular edge, **b** bone involvement, **c** cellular atypia, **d** tumor around nerve

predominantly epithelioid though can occasionally be spindled. The nuclear characteristics are round, hyperchromatic with 'salt and pepper' chromatin clustering. Mitoses are rare, <1 per 10 hpf. Other characteristics including cellular pleomorphism, necrosis (uncommon) and irregular interface with the surrounding soft tissue or bone may be occasionally encountered, however do not predict aggressive behavior (Fig. 2). Notable negatives in PGL include absence of mucin and glands. Background inflammatory changes and embolization material in the vessels may also be encountered on surgical resections.

A second cell population, the sustentacular cell, is spindled surrounding the zellballen and are microscopically inconspicuous. Sustentactular cells will stain for S100 by immunohistochemical evaluation, however so will infiltrating macrophages and Langerhans cells which may be encountered in other tumors in the differential diagnosis (Fig. 1b).

Variants

In a subset of paragangliomas, varied growth patterns can be encountered including trabecular, spindled, angioma-like, and marked sclerosis. When sclerosis/collagen deposition predominates, the neuroendocrine cells become a minor component, and are trapped, appearing irregular mimicking an invasive, malignant neoplasm (Fig. 1c). Careful histologic review and immunohistochemical evaluation utilizing neuroendocrine markers and cytokeratin will allow for the detection of the PGL cells excluding carcinoma. Similarly, highly vascular PGLs may be mistaken for vascular lesions if the background neuroendocrine cell clusters are not appreciated. Alternatively, cellular changes including vacuolization (clear cell change) of the chief cells and/or pigment may create a broader differential diagnosis such as excluding renal cell carcinoma metastases and/or melanoma respectively (Fig. 1d).

Differential Diagnoses

The differential diagnosis for each of the anatomic subsites for PGL should be considered to avoid potential diagnostic errors. Anatomic considerations for carotid body masses include lymph nodes in the neck that may harbor metastatic disease particularly other neuroendocrine tumors (neuroendocrine carcinomas, Merkle cell carcinoma and medullary thyroid carcinoma) though all of these entities will be keratin positive. By imaging, other common entities in the parapharyngeal region where vagal PGLs are encountered include schwannomas, vascular tumors and deep lobe of parotid (salivary tumors), nonetheless histologic evaluation will allow for their distinction. In the middle ear, meningioma, hemangioma, and the middle ear adenoma (which may express neuroendocrine markers but will be keratin

Table 2 Clinicopathologic features of laryngeal paraganglioma versus atypical carcinoid

Features	PGL	Atypical carcinoid
Clinical		
Age	**5th decade**	**6th–7th decade**
Sex (M:F ratio)	**1:3**	**3:1**
Location	Supraglottic (80%)	supraglottic
Symptoms	hoarseness	hoarseness
Metastases	**Uncommon < 6%**	**Frequent metastasis**
Prognosis	**Excellent (influenced by mutational status)***	**50% 5 year survival**
Histologic		
Surface involvement	Absent	Rare
Ulceration	Absent	Uncommon
Cellular pattern	**Orderly**	**Disorganized**
Fibrovascular stroma	Present	Present
Glandular formation	Absent	May be present
Pleomorphism	Infrequent	Mild to marked
Nucleoli	Uncommon	Absent to prominent
Necrosis	Rare	Uncommon
Oncocytic features	Absent	May be present
IHC		
Cytokeratin	−	+
EMA	−	+
CEA	−	+
Chromogranin	+	+
Synaptophysin	+	+
S100	+ sustentacular cells	Caution: infiltrating macrophages/Langerhans cells may stain

IHC immunohistochemical evaluation

*Revised from Ferlito et al. [17]

Values in bold highlight differences between the two groups

positive) should be considered when approaching this anatomic site and possible PGL.

The most problematic area for the correct diagnosis of HNPGLs centers around the larynx and confusion of PGL with atypical carcinoid tumors [17]. Certainly the rarity of laryngeal PGL and diagnosis in the pre-immunohistochemical days may have contributed to this difficulty. In response to this challenge, Dr. Barnes focused on critically reviewing the literature and carefully distinguishing published reports of 'true, confirmed and supported' PGL versus the neuroendocrine carcinomas of the larynx [16]. In 1994, only 54 of over 100 potentially reported cases of laryngeal PGL were deemed as confirmed cases of 'true' PGL of the larynx by Barnes et al. [9]. To further clarify this issue and provide additional resources to the practicing pathologist, a manuscript meticulously comparing atypical carcinoids and PGL arising in the larynx was published [17]. Hallmarks to differentiate laryngeal PGL from atypical carcinoids from this manuscript are highlighted in Table 2. Despite these concerted efforts, the mass literature continued astray. So, Dr. Barnes persisted as the significance of misclassified neuroendocrine carcinomas (atypical carcinoids) as PGL led to erroneous high metastatic rates and clinical characteristics that did not align with PGL in other HN sites. A letter to the editor by Dr. Barnes notes "We had hoped that our recent manuscript (Ferlito *et al*., 1994) would have resolved many of the problematic issues relative to laryngeal PGL. Apparently it has not" [9, 18]. In summation, PGLs of the larynx remain rare with only 76 verified cases in 2004, and importantly the overall metastatic rate of laryngeal PGL on these careful critiques is only 2% [9, 19–21]. With the development and increased use of immunohistochemistry for differentiating tumors, cytokeratin analysis in particular allows for further clarification and distinction of PGL versus NEC of the larynx as long as it is considered in the differential diagnosis.

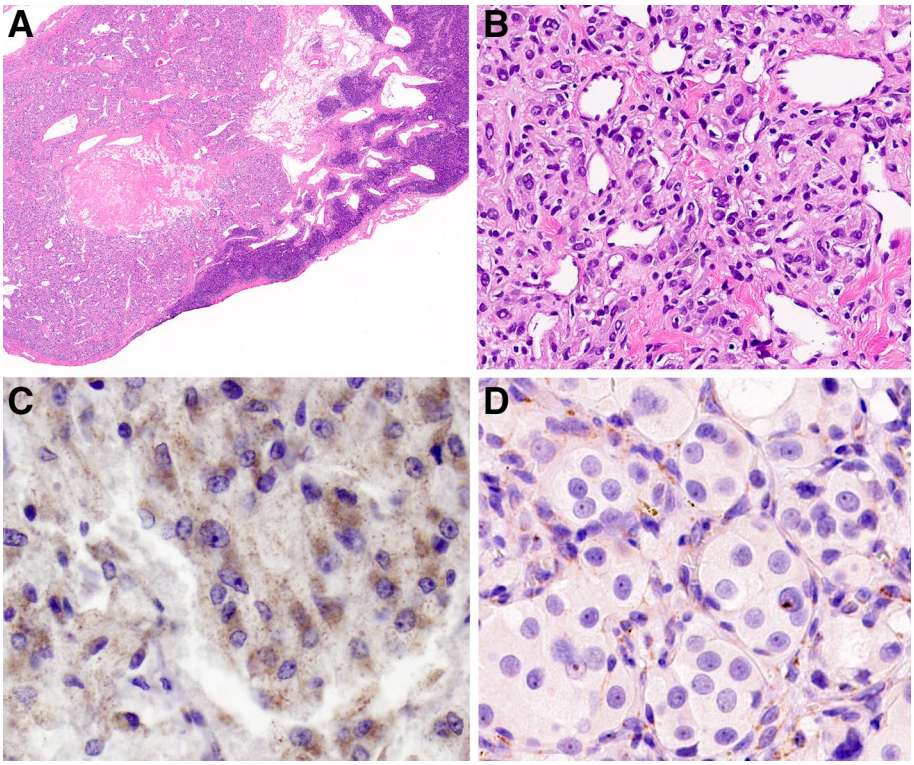


Fig. 3 Metastatic paraganglioma and SDHB immunohistochemical evaluation. **a** A metastatic paraganglioma is present in a lymph node (H&E 10x); **b** the morphology in metastasis is the same as in primary paragangliomas, showing prominent vascularization (H&E 200x). **c** Immunohistochemical evaluation for SDHB expression in a sporadic paraganglioma shows diffuse expression in tumor cells (normal pattern)(400x) compared to **d** SDHB expression loss in a hereditary paraganglioma (note internal control in vascular cells is present)(400x)

Immunohistochemical Evaluation

Diagnosis

The evaluation of HNPGL encompasses imaging to evaluate the site of origin, morphologic HN review and immunohistochemical evaluation based on the differential diagnosis to support lineage. PGL are notably positive for neuroendocrine markers by immunohistochemistry including chromogranin and synaptophysin. Other less specific markers including NSE and CD56 are also expressed. The key differentiation marker is most often cytokeratin to aid in excluding epithelial derived tumors mimicking PGL. S100 will stain the delicate sustentacular cells around the zellballen nests however are not specific and tissue associated macrophages and Langerhans cells may also infiltrate other tumors and stain for S100, a potential pitfall.

Other immunohistochemical markers are evaluated based on the differential diagnostic consideration by morphology and anatomic site.

SDHB Immunohistochemical Evaluation

PGL and other tumor tissues with SDH-deficiency caused by a mutation in any of the SDH family of genes may be screened for utilizing the SDHB immunohistochemical assay [22, 23] (Fig. 3). As the succinate dehydrogenase complex requires all components, mutation in any of these genes (including mutation in SDHAF2) leads to loss of SDHB expression. SDHB should normally be detected in all cells including inflammatory cells and endothelial cells which serve as an internal control. Therefore loss of SDHB expression in the PGL cells is an abnormal finding. Similar loss is seen in SDH-deficient GISTs and RCCs associated with PGL syndromes. Careful documentation that SDHB immunohistochemistry is only a screen tool for the family of SDH genes is important as genetic screening for the altered gene is still required. Studies by van Nederveen et al. and Papathomas et al. confirmed the high sensitivity (84–100%) and specificity (74–85%) of SDHB immunohistochemical evaluation for correlation of loss with genetic alterations [22, 23]. In rare cases of Carney's triad, SDHB immunohistochemical loss may be associated with SDHC methylation and not a hereditary gene mutation [23, 24].

An antibody specific to the SDHA protein shows a pattern of loss specific to tumors with SDHA mutations, with SDHA expression retained in SDHB, SDHC, and SDHD altered tumors [25]. While this marker may aid in evaluation for this specific gene alteration, the rarity of this mutation in the HN, and as SDHB screening is also altered in SDHA mutated tumors, the added utility of SDHA in this cohort may be limited [26]. Antibodies to SDHD protein have also been created which appear to have a screening effect with loss across the SDH complex of genes, similar to SDHB immunohistochemical staining pattern [27].

Table 3 Clinical manifestations and genetic associations within paraganglioma syndromes

	Paraganglioma syndromes				
	PGL1	PGL2[d]	PGL3	PGL4	PGL5
Gene	SDHD[a,b]	SDHAF2[a]	SDHC	SDHB[b]	SDHA
Chromosome	11q23.1	11q12.2	1q23.3	1p36.3	5p15.33
HN presentation	**80–90%**	**75–85%**	**85%**	**25–60%**	**?**
Risk for metastasis	Low < 5%	?	Low < 5%	**30–50%**	?
HNPGL					
Carotid body	**Majority (85%)**	Rare	common	rare	?
Vagal	Common	Very rare	rare	rare	?
Middle Ear	Occur	Reported	?	reported	?
Laryngeal	Reported	?	?	?	?
Multifocality in HN	Usually	Single	Single	?	Single
Other PGL & PHEO					
Sympathetic PGL (thoraco/abdominal)	Common up to 40%	–	Very rare	**Most (50–85%)**	Occur
Adrenal (PHEO)	Up to 50%	–	rare	up to 33%	?
Other occurring tumors					
GIST	Yes (8%)	–	Rare	Yes (14%)	Yes
Renal cell carcinoma	Yes	–	Yes	Yes	Rare
Pituitary adenoma	Yes	–	–	Yes	Yes
Immunohistochemistry [22, 25]					
SDHB[c]	**Lost**	**Lost**	**Lost**	**Lost**	**Lost**
SDHA	Intact	Intact	Intact	Intact	Lost
References	[29, 31]	[29–31]	[29, 31]	[29, 31]	[26, 32]

GIST gastrointestinal stromal tumor; *HN* head and neck; *PGL* paraganglioma; *PHEO* pheochromocytoma; *?* denote information that is not yet known in the literature; values in bold are features of importance to review

[a]Paternal inheritance is required for PGL development, secondary to imprinting of these genes

[b] Rare examples of gene mutations present in sporadic PGL

[c]SDHB may also be lost in tumors from patients with Carney's triad (theorized to be secondary to methylation of SDHC) [24, 39]

[d]There are no other occurring tumors noted in this syndrome

Syndromes and Other Associated Tumors

The causative molecular alterations to define five distinct PGL syndromes have now been elucidated [4]. Table 3 highlights clinical and genomic characteristics specific to each syndrome [28–32].

Paraganglioma syndrome 1 (PGL1) is the most common associated syndrome in HNPGL and is caused by SDHD mutations on Chr 11q23.1. The majority of PGLs with SDHD mutation arise in the carotid body though have been described in all 4 HN sites [29, 31]. The vast majority (80–90%) of individuals with SDHD mutations will have a HNPGL that may be multiple. Additionally, sympathetic PGL and pheochromocytomas (PHEO) also frequently occur in 40–50% of individuals. The awareness of multifocality both above and below the diagram has led to increased screening by imaging in these families. In addition to screening patients for other PGLs, it is now known that SDHD mutations also contribute to gastrointestinal stromal tumors (GIST), a subset of renal cell carcinomas and pituitary adenomas. Histologic features associated with SDH-deficient GIST include epithelioid morphology, multinodular with plexiform involvement of the gastric wall of the stomach predominantly occurring in children and young adults [33]. SDH-deficient RCC shows cuboidal cells with indistinct cell borders vacuolated/bubbly cytoplasm, and monomorphic appearing more eosinophic cells [34, 35]. Whereas SDH-deficient pituitary adenomas were without unique characteristic morphologic features in one study, they showed prominent cellular vacuolization in another [36, 37]. Immunohistochemical evaluation for SDHB can be utilized in these associated tumors and will show loss supporting an SDH-deficient tumor. This is an important adjunct test as a subset of the 10–20% of apparently sporadic HNPGL will be germ-line. This is mostly seen in a subset of patients with SDHD mutations secondary to the

required paternal inheritance of the gene for PGL development described (see Inheritance section).

The defining characteristic of SDHB gene mutations characterizing PGL4 syndrome is the high rate of aggressive disease with ~25% metastatic rate [38]. SDHB mutations can occur in 5–20% of HNPGL with carotid, vagal and middle ear sites being reported, though the majority of SDHB mutated PGL occur in abdominal PGLs (50–85%) and 1/3rd in PHEOs [31]. Caution should be used when evaluating multifocality versus metastases in this cohort by imaging and pathology. Similarly, individuals with germline SDHB mutations are also at risk for GIST, RCC and pituitary adenomas. As SDHB inheritance is autosomal dominant, often a family history is noted.

PGL3 is associated with SDHC mutations found on chromosome 1q23.3. The incidence of families with SDHC is lower than for SDHD however the frequency of HNPGL in this cohort remains high at 75–85%. Carotid body PGLs are also the most common site of occurrence as seen in SDHD cases, however SDHC mutated PGL are typically single in nature without multifocality. In contrast to PGL1, sympathetic PGLs thoraco/abdominal and/or PHEO are also rare. How the distinct succinate family members lead to different tumor presentation remains unclear, though in SDHC affected individuals, renal cell carcinomas may co-occur however GISTs appear rare in frequency compared to SDHD affected individuals. Importantly, PGL from both PGL1 (SDHD) and PGL3 (SDHC) have a low rate for metastasis (<5%).

PGL5 and PGL2 syndromes are rare with less known in regards to specific associations with HNPGLs and other sympathetic PGL and/or PHEO. Caused by SDHA and SDHAF2 mutations respectively, these proteins are also critical for the correct formation of SDH protein complex [30, 32]. Therefore mutations in either of these genes also lead to immunohistochemical protein expression loss of SDHB thereby allowing SDHB antibody to screen for the full range of PGL syndromes (1 through 5).

Carney-Stratakis dyad (Carney-Stratakis syndrome) is the occurrence of PGL with GIST and is not a specific syndrome. As can be seen in Table 3, several different PGL syndromes may share this dyad present in association with mutations in SDHD, SDHC, and SDHB. The histologic features of the SDH-deficient GIST is the same as noted above [33].

Carney's Triad

In Carney's triad, PGL occur with SDH deficient GIST and pulmonary chondroma without a hereditary/genetic link. However, in a recent analysis ~10% were identified to have SDHA, SDHB, or SDHC gene mutations [39]. Moreover, methylation of SDHC gene in a subset of cases can also cause SDH-deficiency. Importantly, evaluation for SDHB will also results in "expression loss" in these tumors as methylation also leads to an altered SDH complex [24, 39]. Thus in the absence of genetic mutations screening for methylation of SDHC may also be considered. Causative defects for the majority of patients remain unknown however genetic screening of these reported regions is advised [24].

Other potentially hereditary syndromes for which HNPGL maybe encountered include neurofibromatosis type I characterized by mutations in NF1, Von Hippel-Lindau (VHL gene), and multiple endocrine neoplasia 2 (RET proto-oncogene). All of these syndromes are autosomal dominant, though may also be encountered in the sporadic setting. All three syndromes may develop PHEO and other tumor types with HNPGL being very rarely encountered [40].

A non-syndromic hereditary mutation in TEMEM127, which is also autosomal dominant leads to a low level of HNPGLs (1–2%) in the carotid body in carriers of this mutation. Similar to other PGL syndromes these individuals may have multiple tumors including thoraco/abdominal PGL and PHEO [41]. To date, risk of metastasis for this mutation appears low.

Outcome/Prognosis

For over 3 decades, Dr. Barnes has brought attention to PGLs. He recognized the need to critically analyze these tumors both histologically and molecularly with an aim to delineate biomarkers of aggressive behavior [42, 43]. The current biologic understanding of PGLs is that they are tumors of indeterminate behavior and should not be classified as benign. No individual or collection of histologic features can predict which HNPGLs will go on to have aggressive behavior and potentially metastasize. By anatomic site, the overall metastatic rate in HNPGLs is noted to vary slightly from 2% in the larynx and middle ear, to 4–6% in carotid body tumors, and up to potentially 16% in vagal PGLs including regional lymph node spread; however multifocality versus true metastases was not clearly delineated in all cases reported [11, 25, 44].

The paradigm shift now is that the significance of the specific genetic alteration present allows for prognostic distinction of risk of aggressive disease (metastases), risk of multifocality and the development of other tumor phenotypes (GIST, RCC, pituitary adenomas). While all SDH genes carry a risk for metastasis, SDHB mutated tumors have the highest rate of metastasis from 30 to 50%. This translates into poor overall survival for this cohort (5 year survival 11–36%) [45, 46]. Moreover, as the number of genes involved in PHEO and sympathetic PGL is even greater in spectrum, next generation sequencing panels for

either germline testing and/or tumor testing particularly in metastatic tumors is advocated by a recent consensus group to aid in defining risk and identifying families in need of further evaluation [47].

Inheritance

Although all of the genes in the PGL syndromes are autosomal dominant, SDHD (PGL1) gene mutations along with SDHAF2 (PGL2) require paternal inheritance [5]. While epigenetic imprinting appears to play a role, further characteristics and the role imprinting plays specific in the biology of this gene remains unclear. For the clinician and pathologist, the significance of paternal inheritance is that a family history of PGL may not be present, however 10–20% of presumed sporadic PGL will be indeed hereditary on genetic testing. Therefore the role of immunohistochemical screening for altered SDH expression may aid in identifying further patients without apparent family history (see immunohistochemical section).

A gap remains as to the contributing factors in the 60% of sporadic HNPGL. As the mutations tightly cluster in key respiratory pathways, further investigations in to other supporting genes in these networks may prove to be informative.

Summary: Changing Times

The clinical approach to HNPGL depends on a number of factors but may include clinical observation, secondary to the potential morbidity of surgery, which places cranial nerves at risk. Previously if by imaging, location, and characteristics were classic, further pathologic assessment such as FNA was not performed secondary to the risk of bleeding in these highly vascular tumors. The shift in characterizing now up to 40% of patients as hereditary and particularly identifying patients who harbor SDHB mutations is questioning the former treatment paradigm [48]. In a series of carotid body PGLs by Ellis et al. patients with SDHB mutations were at higher risk for local/regional recurrence and distant metastases, therefore suggesting earlier surgery and extent of surgery may need to be considered based on mutational status [48].

Moreover while the Endocrine Society Clinical Guidelines Subcommittee (CGS) Task force recommends shared genetic counseling with the patient, resources may limit clinical testing availability [49]. Thus the pathologist is central to highlighting the high rate of hereditary PGL in the HN and can offer potential IHC screening utilizing SDHB studies.

Through immunohistochemical analysis utilizing the SDHB antibody, the family of SDH gene members including the key mutations linked with PGL syndromes 1–5 can be screened for and identified by loss of SDHB expression in the PGL cells. As SDH family of genes is rarely associated with sporadic tumor development, this added information is a strong screening tool to identify individuals at risk, requiring genetic consulting and further testing.

Compliance with Ethical Standards

Conflict of interest The author has no conflicts of interest to declare.

Ethical approval This article does not contain any studies with human participants or animals performed by the author.

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