Head and Neck Pathology (2021) 15:16–24
https://doi.org/10.1007/s12105-021-01292-x

SPECIAL ISSUE: PEDIATRIC PATHOLOGY

Review of Pediatric Head and Neck Neoplasms that Raise the Possibility of a Cancer Predisposition Syndrome

Nahir Cortes-Santiago[1] · **Kalyani Patel**[1]

Received: 11 December 2020 / Accepted: 9 January 2021 / Published online: 15 March 2021

Abstract

Cancer predisposition syndromes (CPS) are generally heritable conditions that predispose individuals to develop cancer at a higher rate and younger age than their representative general population. They are a significant cause of cancer related morbidity and mortality in the pediatric population. Therefore, recognition of lesions that may be associated with a CPS and alerting the clinicians to its implications is a crucial task for a diagnostic pathologist. In this review we discuss benign pediatric head and neck lesions associated with CPS namely: odontogenic keratocyst, juvenile nasopharyngeal angiofibroma, ossifying fibroma of the jaw, paraganglioma, plexiform neurofibroma, plexiform schwannoma, mucosal neuroma, and nevus sebaceous syndrome; along with malignant tumors such as squamous cell carcinoma. Several head and neck melanocytic, endocrine, and central nervous system tumors can also be associated with CPS; they are beyond the scope of this article. Nasal chondromesenchymal hamartoma is discussed elsewhere in this issue.

Keywords Children · Maxilla · Mandible · Oral · Syndrome · Cancer · Benign · Malignant

Introduction

Cancer predisposition syndromes (CPS) are an important cause of morbidity and mortality in children and adolescents. They account for 10% of all cancers, and as the name suggests, confer higher risk of cancer development when compared to the representative general population. Majority of CPS are heritable and occur when the predisposing mutation(s) are passed from parents to offspring, as germline mutations [1]. Rarely, non-heritable CPS can develop in genetic mosaicism where a mutation occurs early in embryogenesis, leading to its presence in a subset of cells [2]. Inherited mutations can function in a dominant or recessive manner, can have different degrees of penetrance, and can cause early or late-onset disease, leading to marked variation in clinical presentation for a given family [3]. Vast majority of CPS genes are tumor suppressors where mutations can lead to loss of function; while about 10% are oncogenes which predispose to cancer via gain of function mutations [4]. Childhood cancer is a relatively rare occurrence, estimated to account for about 1% of all new cancer diagnosis occurring in the United States [5]. In contrast to adults, a significant proportion of pediatric cancers are related to CPS, recognition of which is vital for appropriate follow up, prevention, surveillance and genetic counseling for these patients and their families [6]. Guidelines have been proposed for the identification of patients that would benefit from genetic work-up [7]. These incorporate family history, types of tumors, tumor genetics and comorbidities, among other parameters. Importantly, not all CPS-associated neoplasms are malignant in nature and an understanding of the protean manifestations of these syndromes is paramount to appropriately identify patients that may benefit from genetic work-up and counseling. This review summarizes both benign and malignant lesions of the head and neck region that may raise the possibility of a CPS in the pediatric population.

✉ Kalyani Patel
krpatel@texaschildrens.org

[1] Department of Pathology, Texas Childrens Hospital, 6621 Fannin St, Houston, TX 77030, USA

Benign Pediatric Head and Neck Neoplasms Associated with CPS

Odontogenic Keratocyst (OKC) or Keratocystic Odontogenic Tumor (KCOT)

It is an intraosseous, uni or multicystic tumor arising from the odontogenic epithelium. Per 2005 World Health Organization Classification of odontogenic lesions, OKC is a neoplasm and KCOT is the recommended designation representing its neoplastic nature [8]. They can occur in all age groups and affect mandible more frequently than maxilla. The most common location is the third mandibular molar near the ramus. OKC can be solitary or multiple, and when multiple can be associated with nevoid basal cell carcinoma syndrome (Gorlin-Goltz syndrome). Syndromic OKCs are more common in females, occur in the first decade, more likely multiple and more frequent in the maxillary molar region. They can be the first clue to the clinical diagnosis of Gorlin-Goltz syndrome. Imaging shows a well-defined mostly unilocular radiolucency with smooth margins, with or without an unerupted tooth, and usually without resorption of the adjacent root. Gross examination can vary with the duration of the cyst and secondary infection. Early small cysts are usually unilocular with a smooth, thin wall; older cysts may show a fibrotic or inflamed wall with cheesy contents or pus. Histology is characterized by a stratified squamous epithelium lining a somewhat collagenous cyst wall (Fig. 1a). Surface is typically uneven or corrugated and cyst wall may show secondary changes such as fibrosis, hemosiderin, or lymphocytic inflammation (Fig. 1b).

Gorlin-Goltz syndrome is an autosomal dominant inherited disorder with high penetrance, caused by mutations in PTCH, a tumor suppressor gene mapped to chromosome 9q22.3-q31. It can present with musculoskeletal anomalies and/or tumors. Congenital anomalies include rib anomalies (bifid, splayed, fused), calcification of the falx cerebri and cerebelli, palmar and plantar pits and macrocephaly. Tumorigenesis is seen as basal cell carcinoma, OKC, medulloblastoma, cardiac fibroma, and ovarian fibroma [9].

Juvenile Nasopharyngeal Angiofibroma (JNA)

JNA is seen almost exclusively in adolescent males, accounting for approximately 0.05 to 0.5% of benign pediatric head and neck tumors. They are usually unencapsulated, well-circumscribed, polypoid, and composed of both vascular and fibrous stromal elements. Blood vessels vary in size and calibre. They can be slit-like to ectatic with a staghorn configuration. (Figure 2a) Poorly developed myoid-type cells surround the endothelial lined vascular channels, giving the appearance of a smooth muscle layer. (Figure 2b) A true muscular coat or elastic lamina is not present, a likely explanation for the propensity to bleed with minor trauma. The fibrous stroma can be variably myxoid or collagenous and contains spindle, plump, ovoid, stellate or angular cells. (Figure 2c) These cells are androgen receptor positive and display nuclear reactivity for β-catenin by immunohistochemistry. (Figure 2d) Rare multinucleate cells have been described. Significant cytologic atypia is absent and mitosis is rare. Tumors are usually surrounded by a reactive and/or inflamed epithelium showing respiratory, low cuboidal or metaplastic squamous components. Neural or glandular

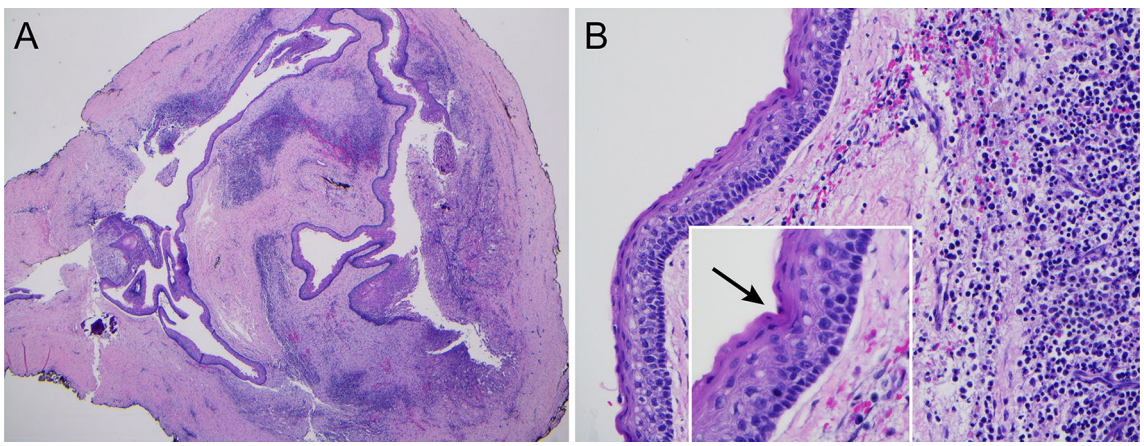

Fig. 1 Odontogenic keratocyst in an 8 year old boy presenting with unerupted tooth and lower jaw pain; and also had a history of craniosynostosis and macrocephaly. **a** Multiloculated cystic neoplasm is seen with mild to moderate lymphocytic inflammation in the cyst wall. (H&E, 40x). **b** Cyst wall is lined by a relatively flat stratified squamous epithelium (H&E, 200x) that shows a corrugated, undulating or wavy surface (inset, arrow). (H&E, 400x)

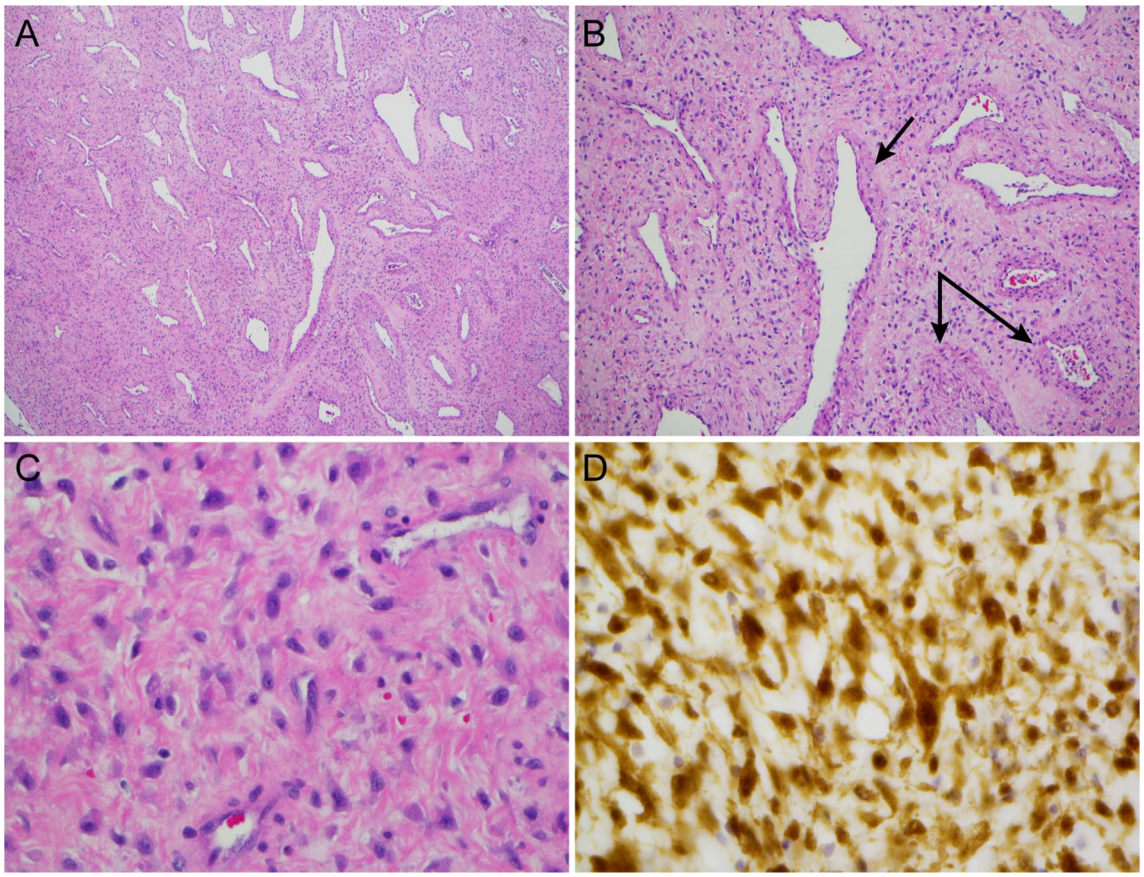

Fig. 2 Juvenile nasopharyngeal angiofibroma in a 14 year old boy. **a** Low power view shows fibrovascular stroma with slit-like to ectatic blood vessels, some of which display a staghorn configuration. (H&E, 40x) **b** Poorly developed perivascular myoid cells (arrows) give impression of a muscular layer. (H&E, 100x). **c** Ovoid, plump spindled cells within the fibrous stroma lack significant cytologic atypia. (H&E, 400x). **d** Beta-catenin immunohistochemistry shows nuclear positivity. (400x)

tissue when present is thought to be entrapped and not neoplastic in nature. While benign in nature, the tumor can be locally aggressive with infiltration into the nose, paranasal sinuses, nasopharynx, and skull base.

The etiology of JNA is not well understood and hormonal influence is thought to play a role. Some studies have reported JNAs to be 25 times more frequent in patients with familial adenomatous polyposis (FAP). [10] Others have shown higher frequency of activating beta catenin mutations in JNAs [11] while some have refuted this finding. [12, 13] Other genetic associations include deletions of chromosome 17, including regions for the tumour suppressor gene p53 as well as the Her-2/neu oncogene, which are altered in many human tumors. [14] Another more recent association is with human papilloma virus and Epstein Barr virus. [15] While the vast majority of JNAs occur in a sporadic manner, it is important to recognize this entity as a possible component of FAP and the possible role of beta catenin mutations in its pathophysiology.

Juvenile Ossifying Fibroma (JOF) of the Jaw

JOF are benign and slow growing tumors arising from the periodontal ligament in molar or pre-molar areas. Microscopically they show cellular fibrous stroma with absent to minimal cytologic atypia intermixed with woven bone showing abundant reactive osteoblasts. Woven bone can often show anastomosing or lattice-like pattern. Mitosis can be seen. Periphery of the lesion shows mature lamellar bone. (Figure 3a, b) Secondary changes such as stromal and/or cystic degeneration, hemorrhage etc. can be seen. Vast majority are sporadic, however about 30% have been reported in patients with hyperparathyroidism jaw tumor syndrome (HPT-JTS). [16] When syndromic, they may be bilateral, multifocal, and may recur. Histopathologic features are not distinctive for syndromic lesions that appear radiolucent compared to the combined radiolucent/radiopaque appearance in sporadic lesions. [17] HPT-JTS patients will have a history of hyperparathyroidism (100%) with or without parathyroid tumors (adenoma/carcinoma), uterine

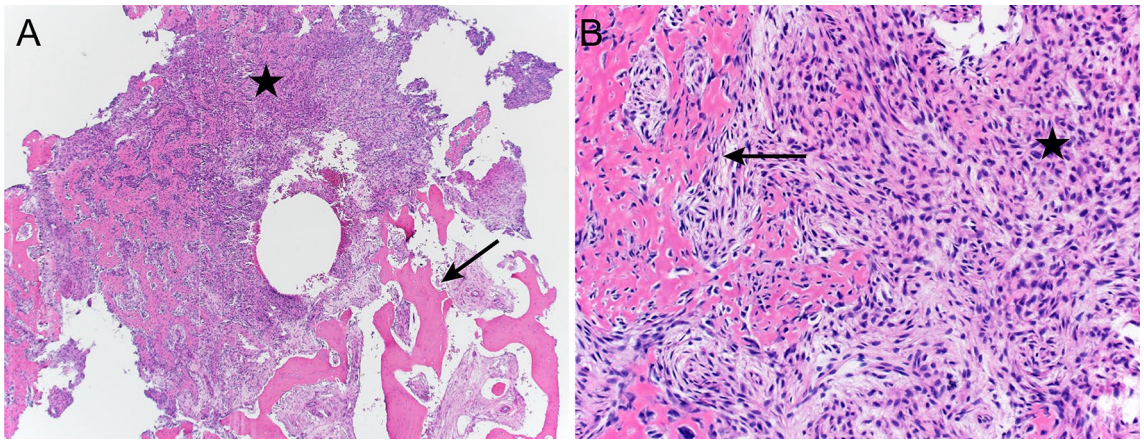

Fig. 3 Juvenile ossifying fibroma of the right maxilla in an 11 year old boy. **a** Low power view shows lesion with peripheral mature lamellar bone (arrow) and central cellular fibro osseous component (*). (H&E, 40x). **b** Central portion of the lesion shows bland fibrous stroma (*) and woven bone with abundant reactive osteoblasts (arrow) (H&E, 200x)

abnormalities and tumors (45%), renal cysts and tumors (15%), and less commonly thyroid, colon, pancreatic and cholangiocarcinomas. [16] HPT-JTS is an autosomal dominant condition caused by mutations in the *HRPT2* gene. [18] CDC73 mutation testing may be recommended in the appropriate clinical context.

Paraganglioma (PGL)

PGLs are neuroendocrine tumors that arise from the sympathetic and parasympathetic paraganglia. Although uncommon in childhood with an incidence of about 0.3 cases per million per year, [19] they (along with pheochromocytomas) are the most common endocrine tumors in children. [20] In the head and neck region they are named by location: carotid body, jugulotympanic (previously called glomus annulare), vagal and laryngeal PGLs. Microscopically, they show round to oval cells with abundant granular eosinophilic cytoplasm with mild-moderate nuclear atypia in Zellballen or trabecular architecture. (Figure 4a–c) Vascular invasion and rare mitotic figures may be seen. Metastasis is the only indicator of malignancy. In an Italian (n = 22) and French (n = 40) study on pediatric paragangliomas, 9% and 22.5% tumors were seen in the head and neck region respectively and about 58% and 78% showed germline mutations in one of the pheochromocytoma paraganglioma (PPGL)

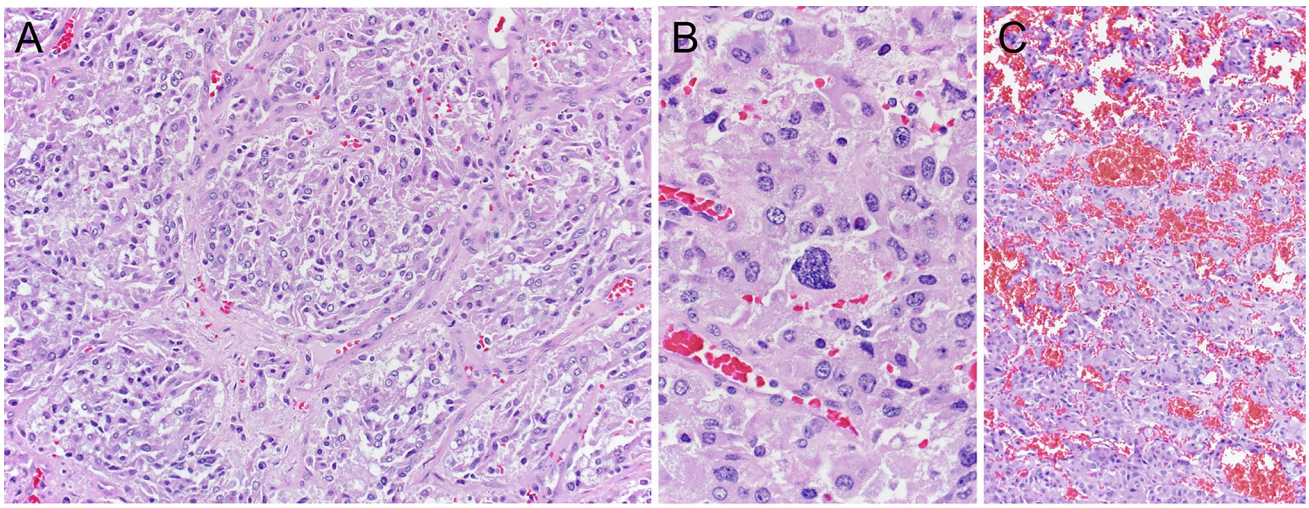

Fig. 4 **a** Paraganglioma of the carotid body in a 12 year old girl. Large polygonal cells with abundant eosinophilic cytoplasm and central round nuclei are seen in Zellballen pattern. (H&E 100X). **b** Abrupt bizarre or anaplastic nuclei with pleomorphism is common (H&E 200X). **c** Tumors are richly vascular with frequent intratumoral acute and remote hemorrhage. (H&E, 200x)

susceptibility genes. [21, 22] SDHB and VHL genes were the most commonly mutated, followed by rare instances in SDHD, HIF2A, SDHC, NF1, and RET. In the French study, incomplete excision and synchronous metastases conferred higher risk for adverse events such as second tumors, local recurrences, metastatic relapses, and death due to disease. However, both studies concluded that identification of a mutation or SDHB status did not have a significant impact on outcome. Notably, succinate dehydrogenase B subunit (*SDHB*) gene germline mutations also predispose to other non-PPGL tumors such as renal cell carcinoma, gastrointestinal stromal tumor and pituitary neoplasia [23].

Plexiform Neurofibromas (PN)

PNs are benign peripheral nerve sheath tumors seen in neurofibromatosis type 1 (NF1). They are thought to be congenital and appear to grow fast in children < 8 years old. [24] Gross appearance is often described as a 'bag of worms' due to their complex, tortuous and convoluted shape. Microscopically, they can be nodular or diffuse and show hypocellular myxoid matrix with Schwann cells, fibroblasts, and mast cells. (Figure 5a–c) Occasional nuclear palisading and rare pigmented cells may be noted. S-100 immunostain shows scattered positivity (in contrast to strong and diffuse staining of a schwannoma) and EMA is positive in the perineurial cells.

NF1 is caused by mutations in the *NF1* tumor suppressor gene located on chromosome 17q11.2, which encodes the protein neurofibromin. Major clinical findings include neurofibromas (including conventional and plexiform types); pigmentary abnormalities (café au lait macules, freckling, Lisch nodules); optic glioma; brainstem glioma; learning, behavioral, and attention deficits; and long bone dysplasia. In addition, affected individuals exhibit an increased risk for developing malignant peripheral nerve sheath tumors and other malignancies [25]. In a study of 59 children with NF1, median age at diagnosis was 2 years with 15% tumors occurring in the head and neck region [26]. About 54% had a history of other tumors including gliomas and malignant peripheral nerve sheath tumors (MPNST).

PNs are characterized by biallelic mutations in the *NF1* gene. Malignant transformation through stepwise progression to atypical neurofibroma can occur in PN and attributes to 45% of MPNST [27, 28]. Atypical neurofibromas show additional frequent loss of CDKN2A/Ink4a/Arf and may be precursor lesions to MPNST [28]. A study of 15 MPNSTs (6 NF1 associated) identified a loss of function somatic alterations of the Polycomb repressive complex 2 (PRC2) components (EED or SUZ12) in 70% of NF1 associated MPNSTs. Tumors with PRC2 loss showed complete loss of H3K27me3 nuclear expression by immunohistochemistry [29]. MPNST is a leading cause of mortality in patients with NF1.

Plexiform Schwannoma (PS)

Schwannomas are benign peripheral nerve sheath tumors originating from the Schwann cells with up to 40% occurring in the head and neck region. PS is a rare variant accounting for only 5% of all schwannomas. Most cases occur in the skin and subcutaneous tissue and show a predilection for the head and neck region, similar to ordinary schwannomas [30]. Head and neck tumors can occur in the vestibular region, oral cavity or as cutaneous lesions. Plexiform schwannomas usually occur in younger adults and are rare in children. Most schwannomas in the head and neck region are sporadic; however, multiple or plexiform tumors suggest a possible association with neurofibromatosis type (NF2) or schwannomatosis.

PS are characterized by intraneural multinodular growth; they are less circumscribed, and often lack a capsule [31]. Microscopically they show a multinodular growth pattern with individual nodules surrounded by a thin fibrous capsule. Nodules are composed of hyper (Antoni A) and hypocellular (Antoni B) areas of slender, elongated, and

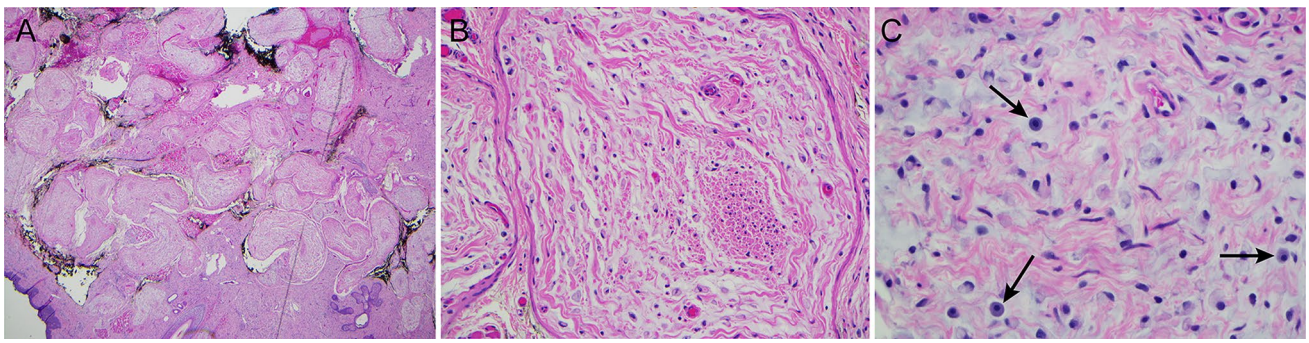

Fig. 5 Plexiform neurofibroma involving the eyelid in a 4 year old girl. **a** Low power view demonstrates multinodular configuration. (H&E, 40x) **b**, **c** Nodules are composed of hypocellular, myxoid stroma containing Schwann cells, fibroblasts and mast cells (arrows). (H&E, 100x and 200x)

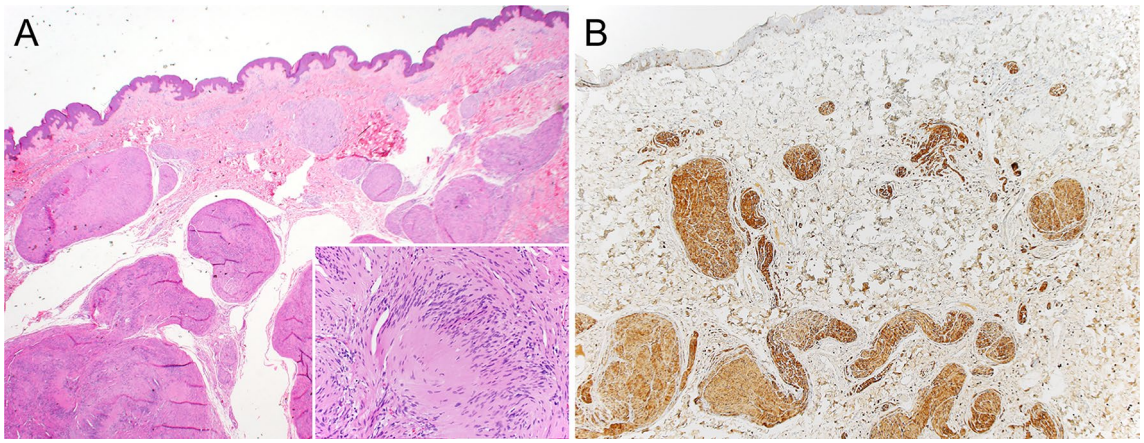

Fig. 6 Plexiform schwannoma in a 17 year old girl. **a** Sub-epidermal multinodular tumor is seen (H&E, 20x) with hypo and hypercellular areas of bland spindle cells in a somewhat fibrillary matrix. (inset, H&E, 200x), **b** Immunostain for S-100 shows diffuse reactivity. (20x)

largely bland spindle cells. Hypercellular areas can show nuclear palisading, called Verocay bodies. Hyalinized and thick-walled vessels are common. Cells are diffusely and strongly positive for S-100 and Sox-10. (Figure 6a, b)

Neurofibromatosis type 2 (NF2) is an autosomal dominant genetic condition caused by mutations in the *NF2* tumor suppressor gene, which is located on chromosome 22 and encodes the protein merlin (schwannomin). It is characterized by the development of schwannomas, meningiomas, ependymomas, low grade gliomas, cerebral calcifications; juvenile posterior subcapsular lenticular opacities and peripheral cortical cataracts; retinal hamartomas; large café au lait macules (typically fewer in number compared to NF1), and bilateral vestibular schwannomas (BVS). BVS are considered the hallmark of this disorder and usually do not develop before adolescence which can delay the diagnosis of NF2. Cutaneous schwannomas can take two forms in NF2: subcutaneous tumors of variable size covered by normal skin or congenital, well-circumscribed brownish plaques, soft on palpation with hypertrichosis. Identification of the latter can facilitate early diagnosis of NF2. [32]

Schwannomatosis is a rare condition associated with mutations in the *LZTR1* and *SMARCB1 (INI1)* genes on chromosome 22. Affected individuals tend to develop peripheral and spinal schwannomas, meningiomas, and chronic pain; however, they do not meet the diagnostic criteria for NF2 (e.g., they exhibit no evidence of vestibular schwannoma or *NF2* mutation) [25, 33]. A study has shown that solitary peripheral schwannomas and NF2-associated vestibular schwannomas retained the immunohistochemical expression of INI1/SMARCB1 in 97–100% of neoplastic cells, while those associated with schwannomatosis showed a mosaic pattern ranging from 10 to 70% of neoplastic cells. The study concluded that partial loss of nuclear INI1/SMARCB1 expression was a reliable marker of schwannomatosis regardless of the involved gene (*SMARCB, LTZR1, NF2*). [34]

Mucosal Neuromas

Mucosal neuromas in the head and neck region can occur in the oral cavity, eyelid or conjunctiva. They are firm, painless, yellowish white, slow growing nodules that show bundles of disorganized and tortuous nerve fibers surrounded by EMA positive perineurium. Histopathologic features can mimic plexiform neurofibromas that lack EMA positive perineurium surrounding the tumor nodules. (Figure 7) Mucosal neuromas have been described in multiple endocrine

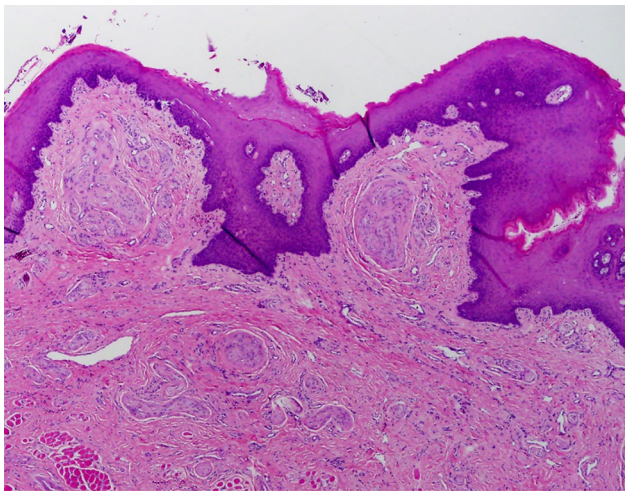

Fig. 7 Mucosal neuroma involving the tongue in a 10 year old girl. Uneven, papillomatous and hyperkeratotic squamous mucosa overlying the lesion. Lesion is sub-epithelial and composed of disorganized bundles of neural tissue. (H&E, 40x) *Photomicrograph courtesy of Dr. John Hicks, MD PhD*

neoplasia type 2B (MEN2B) syndrome. Rare instances of "pure mucosal neuroma syndrome" have also been reported [35] along with cases of neuromas accompanying lipomatosis in patients with PIK3CA inactivating mutations [36].

MEN2B is a rare, but often fatal, hereditary autosomal-dominant cancer syndrome, caused by activating germline mutations in the *RET* proto-oncogene (M918T in about 95% of patients with MEN2B). [37] The syndrome is characterized by early onset medullary thyroid cancer (MTC), pheochromocytoma, and extra endocrine features such as marfanoid habitus, skeletal abnormalities, mucosal neuromas, and ganglioneuromatosis of the gastrointestinal tract. About 90% of patients carry de novo mutations, hence diagnosis of MEN2B may get delayed until late childhood or adolescence when MTC has already developed and/or metastasized. Improved awareness of the early nonendocrine signs of MEN2B, such as mucosal neuromas, can facilitate early diagnosis and intervention. In a study of 38 patients with MEN2B, 35 were sporadic, 22 were diagnosed after an endocrine manifestation at the mean age of 10.6 years but 21 had one or more physician referrals for a MEN2B related feature at a mean of 5 years before the diagnosis. [37]

Nevus Sebaceous and the Nevus Sebaceous Syndrome

Nevus sebaceous is a cutaneous hamartomatous lesion involving epidermis and adnexal structures. It is either congenital or identified in early childhood as a smooth plaque devoid of hair, most commonly in the scalp. Pathologic findings vary with the age of the lesion, as originally described by Mehregan et al., due to lesional components responding to hormonal changes [38]. Epidermal acanthosis and papillomatosis is a relatively constant feature but may become more prominent in older lesions. Sebaceous glands and hair follicles tend to be smaller and underdeveloped in younger

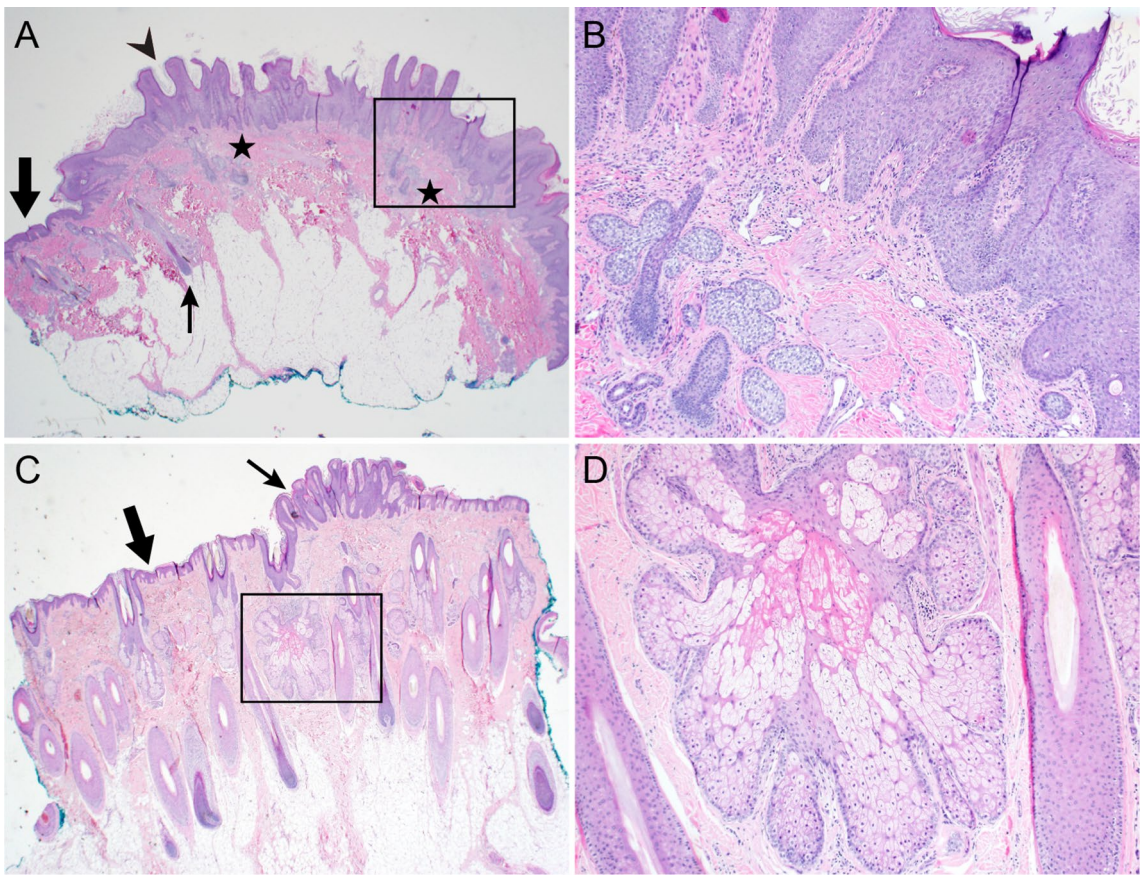

Fig. 8 Nevus sebaceous in an 8 month old infant (panels **a**, **b**) and a 13 year old boy (panels **c**, **d**). **a** Low power view of a skin excision showing non-lesional epidermis (thick arrow) adjacent to a papillomatous lesion (arrow head). Lesional dermis shows malformed and aborted hair follicles (*) that do not reach the underlying fat, in comparison to the adjacent normal ones (thin arrow). (H&E, 20x). **b** An area marked in panel **a**, under medium power, shows an acanthotic epidermis with proliferation of hair follicle cells. Sebaceous glands are not seen. (H&E, 100x). **c** Low power view of a skin excision showing non-lesional epidermis (thick arrow) adjacent to a papillomatous lesion (thin arrow). Lesional dermis shows prominent, malformed and aborted pilosebaceous units. (H&E, 20x). **d** An area marked in panel **c**, under medium power, shows a hyperplastic sebaceous gland with mature hair follicle and a shaft. (H&E, 100x)

lesions whereas older lesions may show sebaceous hyperplasia and have mature hair follicles with well-developed hair shafts (Fig. 8a–d). [39]. Tumors may arise from unresected nevus sebaceous, mostly benign, the most common being trichoblastomas [40, 41]. Once thought to be a relatively common occurrence, malignant transformation is now known to occur rarely with the most common malignancy being basal cell carcinoma. This is exceedingly rare in the pediatric population and prophylactic removal before adolescence is generally not necessary [40]. The vast majority of nevus sebaceous are isolated with an incidence of 1 in 1000 live births and no gender predilection.

The epidermal nevus syndromes are a group of disorders characterized by the presence of epidermal nevi and associated extracutaneous manifestations. The nevus sebaceous syndrome (NSS) is the best known of these disorders and as the name implies it is characterized by the presence of sebaceous nevi. In patients with this syndrome, the cutaneous nevi are associated with neurologic manifestations, most commonly mental retardation and seizures, ocular manifestations such as epibulbar lipodermoid and coloboma and skeletal manifestations [42–45]. Rarely, patients may develop hypophosphatemic, vitamin D-resistant rickets. [46, 47]. The underlying molecular mechanism was unknown until recently *HRAS* or *KRAS* mutations were reported in all of 65 cases of NSS, making it a RASopathy. The mutations were present only in lesional tissue confirming the long time suspected genetic mosaicism [48].

Malignant Pediatric Head and Neck Lesions Associated with CPS

Majority of malignant pediatric head and neck lesions that are associated with CPS are within the central nervous system or endocrine system and are therefore beyond the scope of this review. We discuss the rare occurrence of squamous cell carcinoma of the head and neck in the pediatric population and its possible associations.

Squamous Cell Carcinoma (SCC)

Pediatric SCCs are extremely rare and account for $<1\%$ of pediatric head and neck malignancies. They are associated with previous malignancies, immunosuppressive therapy and/or genetic conditions such as Fanconi anemia (FA), xeroderma pigmentosum and keratitis ichthyosis and deafness syndrome [49]. They are rarely associated Epstein-Barr virus and human papilloma virus, which in turn can confer increased risk to development of other tumors [50]. Oral cavity is the most common location followed by larynx [51] and treatment by wide resection is favored over resection followed by radiotherapy. They are staged using the adult literature and staging system. Due to the rarity of this disease, there is no definitive data on difference in prognosis when compared to stage matched adult tumors.

Concluding Remarks

This review includes benign and malignant pediatric neoplasms largely within the soft tissue compartment of the head and neck region that may be associated with CPS. There are other entities in the endocrine, ophthalmic, and central nervous systems that may be associated with a CPS. They are beyond the scope of this article. While many of these associations are rare, recognition of their existence is crucial for early identification of patients that may benefit from a more thorough diagnostic work up including genetic studies and counseling.

Acknowledgements We would like to thank the editors for this opportunity to create a concise review article on the relationship between the pediatric head and neck lesions and their associated cancer predisposition syndromes and hope it will serve as a valuable reference for practicing pathologists. We sincerely thank Ms. Karen Prince, graphics designer for her expertise in creating the illustrations for this article. We also thank Dr. John Hicks, MD PhD for the illustration of the mucosal neuroma as Fig. 7.

Compliance with Ethical Standards

Conflict of interest There is no conflict of financial or other interests for both the authors.

Ethical approval This work was conducted after appropriate approval from the Institutional Review Board (IRB) for the conduct of ethical research on human material. Under the IRB H-36163 used for this study, the consent is waived for the subjects involved, due to the retrospective nature of the study.

References

1. Anderson DE. The role of genetics in human cancer. CA Cancer J Clin. 1974;24(3):130–6.
2. Vijg J. Somatic mutations, genome mosaicism, cancer and aging. Curr Opin Genet Dev. 2014;26:141–9.
3. Frank SA. Genetic predisposition to cancer - insights from population genetics. Nat Rev Genet. 2004;5(10):764–72.
4. Dixit A, et al. Sequence and structure signatures of cancer mutation hotspots in protein kinases. PLoS ONE. 2009;4(10):e7485.
5. Ward E, et al. Childhood and adolescent cancer statistics, 2014. CA Cancer J Clin. 2014;64(2):83–103.
6. Zhang J, et al. Germline mutations in predisposition genes in pediatric cancer. N Engl J Med. 2015;373(24):2336–46.
7. Ripperger T, et al. Childhood cancer predisposition syndromes: a concise review and recommendations by the Cancer Predisposition Working Group of the Society for Pediatric Oncology and Hematology. Am J Med Genet A. 2017;173(4):1017–37.
8. Barnes L. Pathology and genetics of head and neck tumors: World Health Organization, International Agency for Research on Cancer. Lyon (France): IARC Press; 2007.

9. Fujii K, Miyashita T. Gorlin syndrome (nevoid basal cell carcinoma syndrome): update and literature review. Pediatr Int. 2014;56(5):667–74.
10. Giardiello FM, et al. Nasopharyngeal angiofibroma in patients with familial adenomatous polyposis. Gastroenterology. 1993;105(5):1550–2.
11. Abraham SC, et al. Frequent beta-catenin mutations in juvenile nasopharyngeal angiofibromas. Am J Pathol. 2001;158(3):1073–8.
12. Guertl B, et al. Nasopharyngeal angiofibroma: an APC-gene-associated tumor? Hum Pathol. 2000;31(11):1411–3.
13. Klockars T, et al. Juvenile nasopharyngeal angiofibroma: no evidence for inheritance or association with familial adenomatous polyposis. Fam Cancer. 2010;9(3):401–3.
14. Schick B, et al. p53 and Her-2/neu in juvenile angiofibromas. Oncol Rep. 2005;13(3):453–7.
15. Mishra A, et al. Human Papilloma virus in Juvenile Nasopharyngeal Angiofibroma: possible recent trend. Am J Otolaryngol. 2016;37(4):317–22.
16. Torresan F, Iacobone M. Clinical features, treatment, and surveillance of hyperparathyroidism-jaw tumor syndrome: an up-to-date and review of the literature. Int J Endocrinol. 2019;2019:1761030.
17. Aldred MJ, et al. Dental findings in a family with hyperparathyroidism-jaw tumor syndrome and a novel HRPT2 gene mutation. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2006;101(2):212–8.
18. Carpten JD, et al. HRPT2, encoding parafibromin, is mutated in hyperparathyroidism-jaw tumor syndrome. Nat Genet. 2002;32(4):676–80.
19. Waguespack SG, et al. A current review of the etiology, diagnosis, and treatment of pediatric pheochromocytoma and paraganglioma. J Clin Endocrinol Metab. 2010;95(5):2023–37.
20. Ross JH. Pheochromocytoma: special considerations in children. Urol Clin North Am. 2000;27(3):393–402.
21. Virgone C, et al. Pheochromocytomas and paragangliomas in children: data from the Italian Cooperative Study (TREP). Pediatr Blood Cancer. 2020;67(8):e28332.
22. de Tersant, M., et al., Pheochromocytoma and Paraganglioma in Children and Adolescents: Experience of the French Society of Pediatric Oncology (SFCE). J Endocr Soc, 2020. **4**(5): p. bvaa039.
23. Niemeijer ND, et al. The phenotype of SDHB germline mutation carriers: a nationwide study. Eur J Endocrinol. 2017;177(2):115–25.
24. Dombi E, et al. NF1 plexiform neurofibroma growth rate by volumetric MRI: relationship to age and body weight. Neurology. 2007;68(9):643–7.
25. Chi, A.C., B.W. Neville, and L. Cheng, Plexiform schwannoma of the oral cavity: report of eight cases and a review of the literature. Head Neck Pathol, 2020.
26. Kim A, et al. Characteristics of children enrolled in treatment trials for NF1-related plexiform neurofibromas. Neurology. 2009;73(16):1273–9.
27. Rodriguez FJ. Peripheral nerve sheath tumors: the elegant chapter in surgical neuropathology. Acta Neuropathol. 2012;123(3):293–4.
28. Chaney KE, et al. Cdkn2a Loss in a Model of Neurofibroma Demonstrates Stepwise Tumor Progression to Atypical Neurofibroma and MPNST. Cancer Res. 2020;80(21):4720–30.
29. Lee W, et al. PRC2 is recurrently inactivated through EED or SUZ12 loss in malignant peripheral nerve sheath tumors. Nat Genet. 2014;46(11):1227–32.
30. Berg JC, et al. Plexiform schwannoma: a clinicopathologic overview with emphasis on the head and neck region. Hum Pathol. 2008;39(5):633–40.
31. Antonescu CR, S.B.a.W.J., Tumors of the peripheral nervous system 4th edition ed. Atlas of tumor pathology (AFIP). 2012: Silver Spring, MD: American Registry of Pathology.
32. Castellanos E, et al. Early genetic diagnosis of neurofibromatosis Type 2 from skin plaque plexiform schwannomas in childhood. JAMA Dermatol. 2018;154(3):341–6.
33. Merker VL, et al. Clinical features of schwannomatosis: a retrospective analysis of 87 patients. Oncologist. 2012;17(10):1317–22.
34. Caltabiano R, et al. A mosaic pattern of INI1/SMARCB1 protein expression distinguishes Schwannomatosis and NF2-associated peripheral schwannomas from solitary peripheral schwannomas and NF2-associated vestibular schwannomas. Childs Nerv Syst. 2017;33(6):933–40.
35. Owens M, et al. SOS1 frameshift mutations cause pure mucosal neuroma syndrome, a clinical phenotype distinct from multiple endocrine neoplasia type 2B. Clin Endocrinol (Oxf). 2016;84(5):715–9.
36. Briand, C., et al., Congenital infiltrating lipomatosis of the face with lingual mucosal neuromas associated with a PIK3CA mutation. Pediatr Dermatol, 2020.
37. Makri A, et al. Multiple endocrine neoplasia type 2B presents early in childhood but often is undiagnosed for years. J Pediatr. 2018;203:447–9.
38. Mehregan AH, Pinkus H. Life history of organoid nevi: special reference to nevus Sebaceus of Jadassohn. Arch Dermatol. 1965;91:574–88.
39. Solomon LM, Esterly NB. Epidermal and other congenital organoid nevi. Curr Probl Pediatr. 1975;6(1):1–56.
40. Idriss MH, Elston DM. Secondary neoplasms associated with nevus sebaceus of Jadassohn: a study of 707 cases. J Am Acad Dermatol. 2014;70(2):332–7.
41. Cribier B, Scrivener Y, Grosshans E. Tumors arising in nevus sebaceus: a study of 596 cases. J Am Acad Dermatol. 2000;42(2 Pt 1):263–8.
42. Diven DG, et al. Nevus sebaceus associated with major ophthalmologic abnormalities. Arch Dermatol. 1987;123(3):383–6.
43. Gurecki PJ, et al. Developmental neural abnormalities and seizures in epidermal nevus syndrome. Dev Med Child Neurol. 1996;38(8):716–23.
44. Rogers M. Epidermal nevi and the epidermal nevus syndromes: a review of 233 cases. Pediatr Dermatol. 1992;9(4):342–4.
45. Happle, R., The group of epidermal nevus syndromes Part I: Well defined phenotypes. J Am Acad Dermatol, 2010. **63**(1): p. 1–22; quiz 23-4.
46. Kishida ES, et al. Epidermal nevus syndrome associated with adnexal tumors, spitz nevus, and hypophosphatemic vitamin D-resistant rickets. Pediatr Dermatol. 2005;22(1):48–54.
47. Zutt M, et al. Schimmelpenning-Feuerstein-Mims syndrome with hypophosphatemic rickets. Dermatology. 2003;207(1):72–6.
48. Groesser L, et al. Postzygotic HRAS and KRAS mutations cause nevus sebaceous and Schimmelpenning syndrome. Nat Genet. 2012;44(7):783–7.
49. Sidell D, et al. Pediatric squamous cell carcinoma: case report and literature review. Laryngoscope. 2009;119(8):1538–41.
50. Llewellyn CD, Johnson NW, Warnakulasuriya KA. Risk factors for squamous cell carcinoma of the oral cavity in young people: a comprehensive literature review. Oral Oncol. 2001;37(5):401–18.
51. Dombrowski ND, et al. Squamous cell carcinoma of the head and neck in children. Int J Pediatr Otorhinolaryngol. 2019;117:131–7.