Pediatric Surgical Pathology of Branchial and Congenital Anomalies of the Head and Neck

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Introduction

Ninety percent of neck masses in children are benign. A large review in the 1980s [1] found that 55% were congenital lesions, 27% were inflammatory lesions, 5% were noninflammatory benign masses, 3% were benign neoplasms, and 11% were malignancies. The preoperative diagnosis was correct in 61% of patients. The same percentage of malignancy is reported by others [2], although the percentage varies among countries. The distribution of neck masses in children has been shown to be 45% congenital, 40% inflammatory, 12% benign, and 3% malignant [3].

Branchial Cleft Anomalies

The branchial apparatus consists of four pairs of arches separated by four paired grooves externally and four paired pouches internally. The external grooves are called branchial clefts, and the internal pouches are known as pharyngeal pouches.

Definition: Anamalies may be of the first, second, third, or fourth branchial arches. Branchial anomalies comprise cysts, fistulae, and sinuses and result from incomplete obliteration of the clefts and pouches, and duplication of the first branchial cleft.

Clinical Presentation: (Refer to Chap. 14 for each individual presentation). Branchial cleft anomalies represent the most common congenital lateral neck mass and are second only to thyroglossal cysts when the whole neck is considered [4]. Ninety percent of all branchial cleft cysts and sinuses originate in the second branchial arch.

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Hereditary/Genetic Factors: Rare cases are inherited as part of the branchio-oculo-facial syndrome, an autosomal dominant disorder with variant expression [5] due to mutations involving the TFP2A gene.

Classification: Classified according to the branchial cleft involved.

First Branchial Cleft Anomalies: These accounts for around 8–18% [6, 7]; approximately 68% are cysts, 16% are sinuses, and 16% are fistulas.

Clinical Presentation: Refer to Chap. 14.

Classification: First branchial anomalies are classified in two subgroups. Type 1 defects are duplication anomalies of the membranous external auditory canal and are typically sited medially, inferiorly, or posteriorly to the concha and pinna. Type 2 anomalies are derived from the first branchial cleft and the first and second branchial arches and are thought to represent duplications of the auditory canal and the pinna and present as preauricular, infra-auricular, or postauricular swellings.

Microscopic Features: Type 1 defects are duplication anomalies of the membranous external auditory canal and contain only ectodermal elements. They are often confused on histological examination with epidermoid cysts. The fistula may show associated parotid tissue, and lymphoid tissue is common. Type 2 defects show ectodermal and mesodermal components showing keratinizing squamous epithelium with adnexal structures and cartilage [8]. Figures 15.1a and b. However, it may not be possible to distinguish between type 1 and type 2 lesions [9].

Differential Diagnosis: Type 1 differential diagnosis is epidermoid cyst. Type 2 differential diagnosis are dermoid cysts and cystic sebaceous lymphadenoma of the parotid gland, a tumor rarely found in children [10].

Second Branchial Cleft Anomalies: These are the most frequent anomalies of the branchial clefts accounting for 69–95% of all anomalies [7]. The usual location is in the lateral neck, anterior to the sternocleidomastoid muscle, most present near the angle of the mandible.

Clinical Presentation: Refer to Chap. 14.

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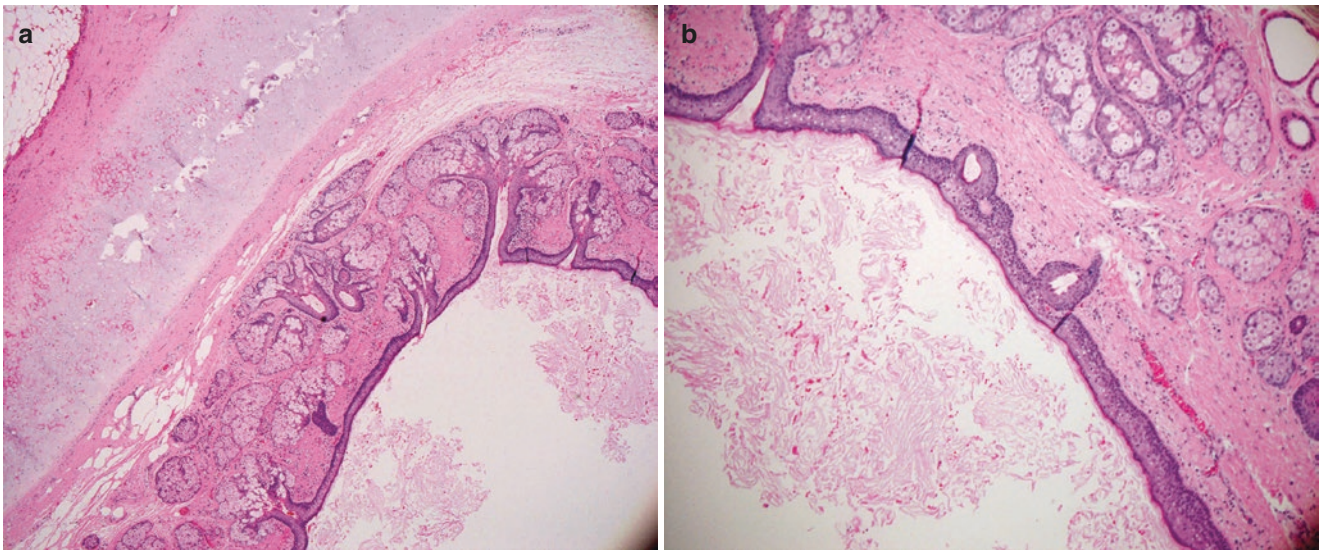

Fig. 15.1 Type 2 first branchial cleft anomaly. Note the presence of ectodermal and mesodermal components, with squamous epithelium, adnexal structures, and cartilage. (**a**) H&E × 10; (**b**) H&E × 20)

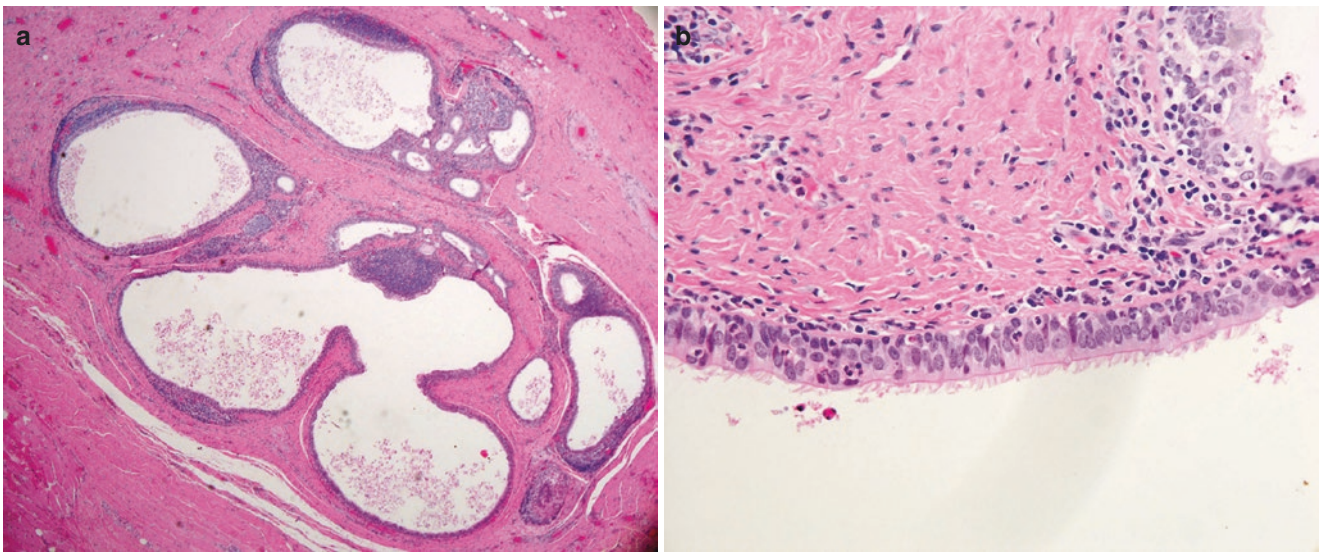

Fig. 15.2 Second branchial cleft anomaly with lymphoid tissue within the wall and lined by respiratory type epithelium. (**a**) low power view H&E × 4. (**b**) higher power H&E × 20)

Classification: There are four subgroups depending on their location (see Chap. 14).

Microscopic Features: Cysts are three times more common than fistulas. The cysts are lined by squamous epithelium (90%), respiratory type epithelium (8%) or both (2%) [11]. Figures 15.2a and b. The cyst content may be keratin, mucus, or serous material, and it may contain cholesterol or purulent material. There may be fibrosis of the wall due to repeated infections; in these cases, the epithelium may be partially replaced by granulation tissue or fibrosis. The majority show lymphoid tissue with or without germinal centers within the wall. Ectopic salivary gland tissue [12] and xanthogranulomatous inflammation have been described in adults [13].

Differential Diagnosis: Lateral Thyroglossal Duct Cyst.

Third and Fourth Branchial Pouch Anomalies: These are rare, comprising 3–10% of branchial anomalies [14]. Failure to close the third or fourth branchial pouch results in cysts or sinuses in close proximity or inside the thyroid gland. When present, the sinus tract originates in the pyriform fossa. These remnants tend to occur on the left side. These anomalies may be dangerous in neonates due to rapid enlargement producing respiratory distress due to airway compression [15].

Clinical Presentation: Refer to Chap. 14.

Microscopic Features: Cyst may be lined by squamous or respiratory type epithelium and may show thyroid and thymic tissue [16].

Differential Diagnosis: Cysts arising from thymic or parathyroid rests, which are not connected to the pyriform sinus.

Congenital Midline Cervical Cleft: Rare congenital anomaly considered to be due to impaired fusion of the distal branchial arches in the midline. The cleft may extend from the submental region to the suprasternal notch [17].

Clinical Presentation: Refer to Chap. 14.

Microscopic Features: The sinus tract is lined by respiratory type epithelium and seromucinous glands. The skin over the tract shows parakeratosis and absent adnexal structures. Bundles of striated muscle are seen in the dermis [18].

Cervical Thymic Remnants and Cysts

Definition: The thymic primordia originate in the third branchial pouches at the end of the fourth week. The bilateral thymic primordia elongate and descend along the thymopharyngeal tracts until the fusion in the midline at the eighth week, continuing to migrate down into the superior mediastinum [19]. Cervical thymic cysts are thought to arise from remnants of the thymopharyngeal duct that fail to involute.

Clinical Presentation: Refer to Chap. 14.

Macroscopical Features: Ectopic cervical thymus presents as a soft and well encapsulated mass. Thymic cyst may present as a sinus tract or cystic structure and are more common [20].

Microscopic Features: Ectopic cervical thymus may show normal thymus tissue, atrophic thymus, or giant cell reaction with cholesterol clefts [21]. Cysts are lined by stratified squamous, columnar, or cuboidal epithelium with or without secondary changes (granulation tissue, fibrosis, and cholesterol clefts). The wall shows thymic tissue with lymphoid component and Hassall's corpuscles [20]. Parathyroid tissue may be found embedded within ectopic thymus tissue and in the wall of thymic cysts [22].

Thyroglossal Duct Cyst

Definition: Thyroglossal duct cysts are the most frequent congenital abnormality in children accounting for 70–75% of midline neck swelling in children [23]. The thyroid primordium develops at the end of the fourth week of gestation as a small solid mass of endoderm proliferating at the foramen cecum, which lies at the junction of the anterior two thirds and posterior third of the tongue. The thyroid primordium descends ventral to the developing hyoid bone and laryngeal cartilages maintaining its attachment to the foramen cecum via the thyroglossal duct. The thyroid reaches its final position at the seventh week of gestation and the thyroglossal duct normally involutes between the seventh and tenth week of gestation [24].

Clinical Presentation: Refer to Chap. 14.

Classification: According to location (a) intralingual, (b) suprahyoid or submental, (c) thyrohyoid, and (d) suprasternal.

Macroscopic Features: A long duct-like structure is generally submitted for examination, usually attached to a portion of the hyoid bone. Ideally, the duct should be bisected longitudinally still attached to the hyoid bone (which needs to undergo decalcification) to see the relationship between them. Cysts may measure up to 10 cm, although generally are less than 3 cm in diameter.

Microscopic Features: The lining of the duct may be squamous or respiratory type epithelium, sometimes with salivary or thyroid gland tissue in the wall. Lymphoid tissue may be identified. Stratified squamous epithelium tends to be closer to the foramen cecum, and thyroid acinar epithelium tends to be proximal to the thyroid gland. The lining may be replaced by inflammatory granulation tissue and fibrosis if there has been infection. The incidence of finding thyroid tissue is up to 40% when serial sections are done [25]. Figure 15.3.

Histological examination of the decalcified hyoid bone may show the tract extending into the bone. Rare cases of papillary thyroid carcinoma developing in the wall of a thyroglosal duct cyst have been reported [26].

Differential Diagnosis: Branchial cleft cyst, as the epithelial lining can be identical and lymphoid tissue may be present in a thyroglossal duct cyst. Clinicopathological correlation regarding the site and the relationship to the hyoid bone is significant for the diagnosis.

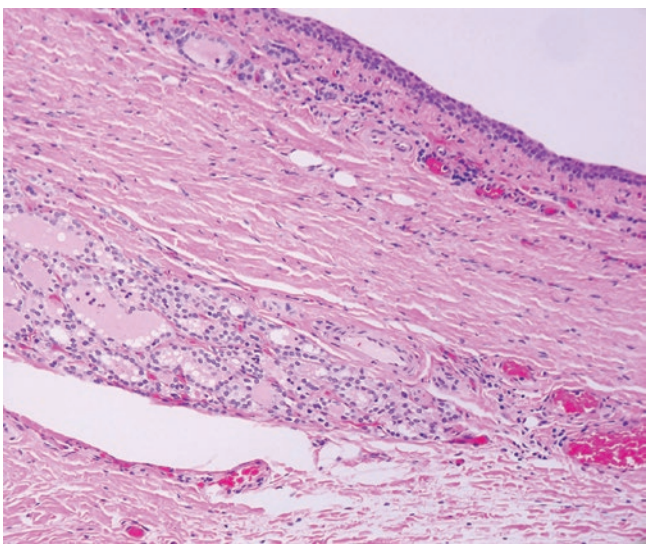

Fig. 15.3 Thyroglossal duct lined by epithelium and with presence of thyroid follicles in the wall (H&E × 20)

Foregut (Enteric) Duplication Cysts (Floor of the Mouth Developmental Cyst)

Definition: Foregut duplication cysts (FDCs) are uncommon developmental lesions, which arise from the embryonic foregut, which gives rise to the pharynx, lower respiratory tract, and upper gastrointestinal tract [27, 28]. FDCs are regarded as choristomas and are thought to arise from persisting heterotopic rests.

In the tongue, they are believed to arise from endodermal cells that become trapped during the fusion process [29].

Based on their epithelial type and other features, foregut duplication cysts may resemble airway, esophagus, or small intestine. Therefore, the term foregut duplication cyst includes bronchogenic cyst, esophageal duplication cyst, and enteric duplication cyst [27, 28, 30].

Clinical Presentation: They are most frequently seen in the thorax or abdomen but most uncommon in the head and neck. They may arise in the oral cavity including the tongue, oropharynx, supraglottis, intra- or extralaryngeal, anterior midline, supralateral neck, or paraspinally [28, 31]. The Foregut cysts can present shortly after birth and can even be detected antenatally [32]. Although most present asymptomatically, the specific location may cause respiratory and/or feeding difficulties [33].

Macroscopic Features: Foregut cysts present as thin-walled cysts with serous or mucoid fluid content. A large study on head-and-neck FGCs in children identified an average size of 1.4 cm, with a range of 0.5–8.5 cm [27].

Microscopic Features: Histologically, foregut cysts are lined by epithelium, which can be a mixture of squamous epithelium, ciliated respiratory epithelium, and/or gastrointestinal-type epithelium. Variable amounts of parietal cells may be seen [33, 34]. Smooth muscle is usually identified surrounding the cyst. Figures 15.4a and b. Those cysts that are lined by ciliated respiratory-type epithelium and include seromucinous respiratory glands are classified as *bronchogenic cysts*. The cyst wall contains smooth muscle, but cartilage is rarely seen in cervical bronchogenic cysts. Lymphoid tissue when present is scanty and focal [34, 35].

Differential Diagnosis: Ranula, lymphangioma, hemangioma, thyroglossal cyst, and dermoid cyst [33, 36, 37]. Foregut cysts are distinguished from a teratoma by lack of tissues other than the ones mentioned; from a dermoid cyst by the lack of skin appendages; from a branchial cleft cyst by the presence of smooth muscle, seromucous glands, scanty lymphoid tissue, and cartilage if present and from a thyroglossal duct cyst by the presence of smooth muscle and the absence of thyroid tissue [38].

Cervical Chondrocutaneous Remnant

Definition: Congenital benign small neck masses similar to preauricular tags but located in the lateral neck. They are probably remnants of the first or second branchial arch [39] and are generally unilateral. They are always present at birth. They are also referred to as cervical skin tag, accessory tragus, or cervical auricle.

Clinical Presentation: Refer to Chap. 14

Hereditary/Genetic Features: Frequently associated with other anomalies, may be part of the branchio-ocular-facial syndrome.

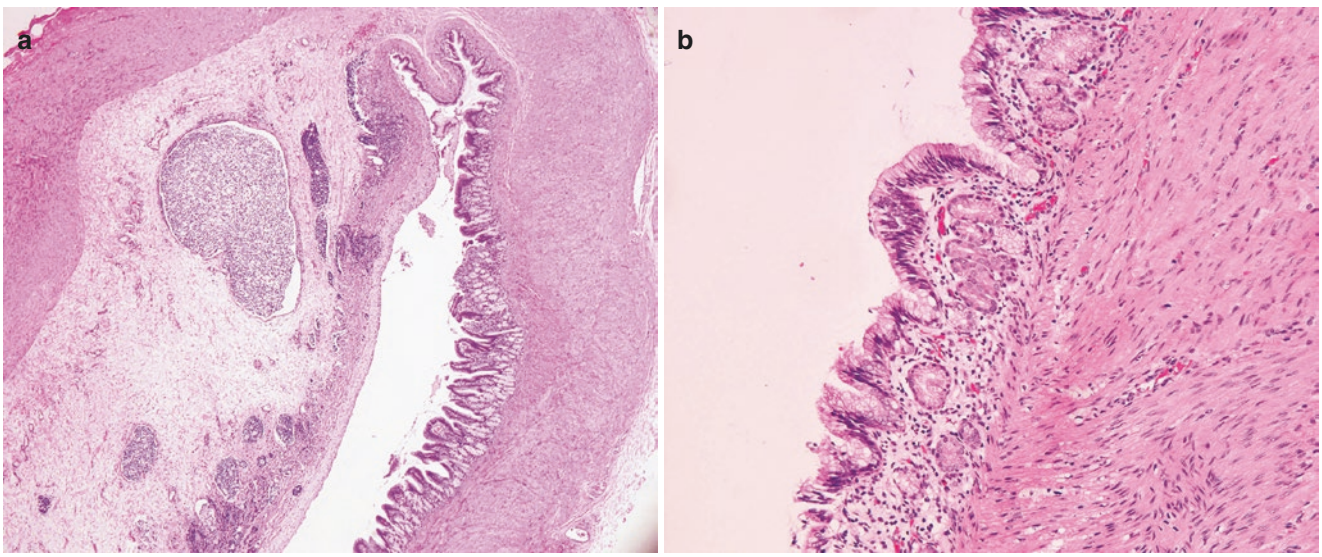

Fig. 15.4 (**a**) Enteric duplication cyst lined by colonic type mucosa and with presence of submucosa and muscularis propria (H&E × 4). (**b**) Higher magnification shows colonic type mucosa with presence of goblet cells (H&E × 20)

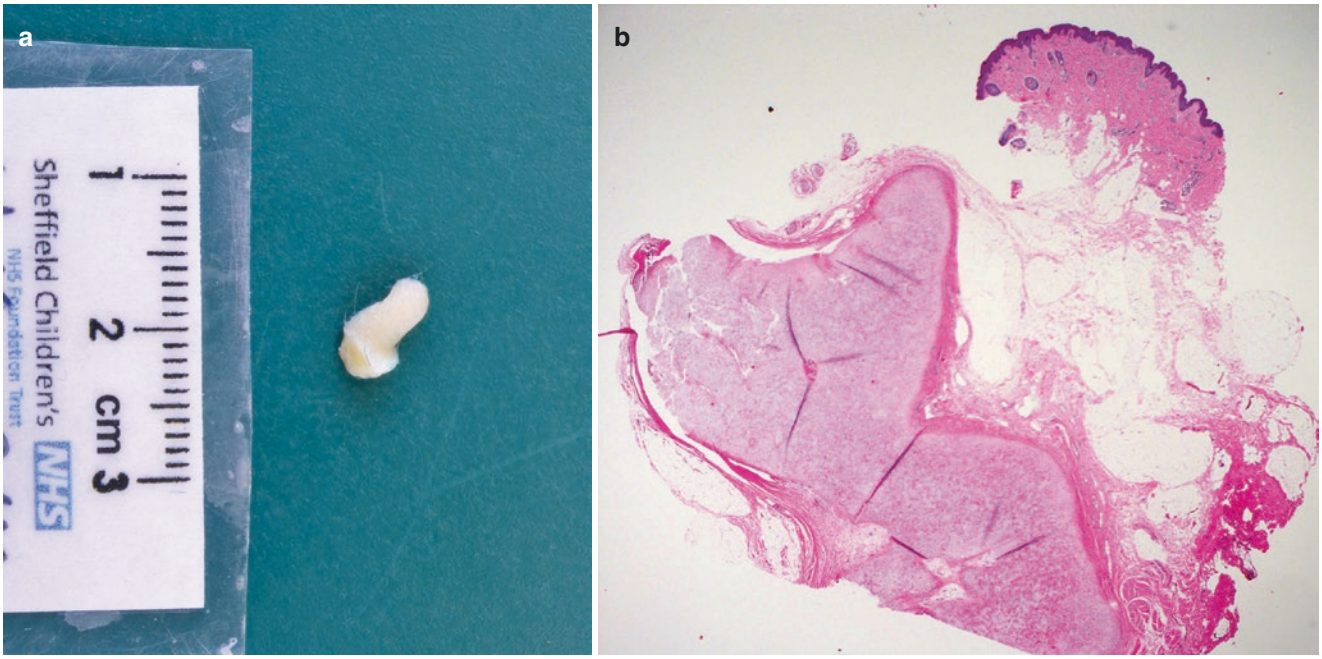

Fig. 15.5 (**a**) Chondrocutaneous remnant in the neck, covered by normal looking skin. (**b**) the histology shows a central core of cartilaginous tissue (H&E × 4)

Macroscopy: Small pedunculated mass covered by skin with a central cartilage core. Figure 15.5a.

Microscopy: Normal skin over a cartilage core which may be hyaline or elastic in type. Figure 15.5b.

Heterotopic Salivary Glands

Definition: Salivary gland tissue outside the major or minor salivary glands. Thought to arise as a consequence of a defective closure of the precervical sinus of His within the branchial apparatus followed by abnormal differentiation of cells into salivary glandular structures within the ectodermal lining of the sinus [40].

Clinical Presentation: Typically present at birth or in childhood as a draining sinus and/or an asymptomatic nodule in the neck along the lower anterior sternocleidomastoid muscle [41].

Microscopy: Duct lined by pseudostratified columnar epithelium with adjacent lobules of serous, mucinous, or seromucinous salivary gland tissue embedded in connective subcutaneous tissue. Benign and malignant tumors arising from cervical heterotopic salivary glands have been reported in children including Warthin's tumor, pleomorphic adenoma, and mucoepidermoid carcinoma [42].

Nasolabial Cysts

Definition: Benign nonodontogenic cyst in the anterior maxillary region. Considered to be a remnant of the embryonic nasolacrimal duct or the lower anterior portion of the mature duct [43].

Clinical Presentation: The cyst presents near the base of the nostril or in the superior aspect of the upper lip and is generally unilateral. Unusual in children, more common in black females.

Microscopy: Cyst lined by respiratory type, squamous or simple cuboidal epithelium, or a combination of these.

Dermoid Cyst

Definition: Dermoid cysts are developmental malformations lined by orthokeratinized squamous epithelium and contains adnexal structures (hair follicles, sebaceous glands, eccrine glands) in the cyst wall. The lumen contains variable amount of keratinous material [28, 44].

Clinical Presentations: Approximately 7% of all dermoid cysts occur in the head and neck region [44]. In this area, they more commonly arise in the midline of the floor of the mouth and as a midline nasal mass [44, 45]. A study investigating 49

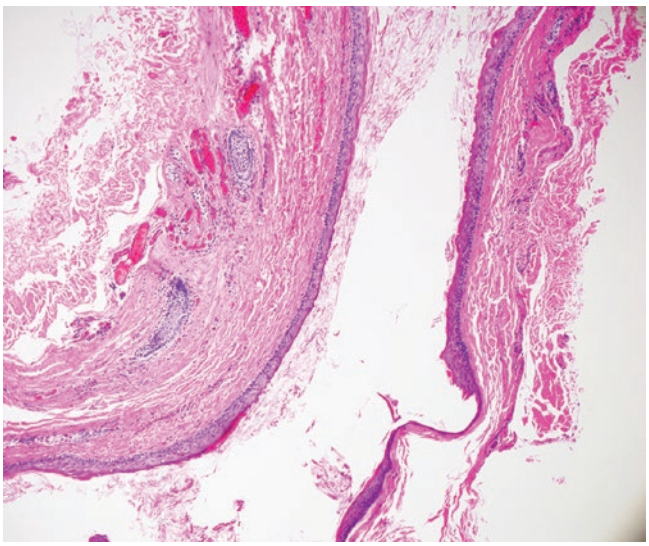

Fig. 15.6 Dermoid cyst lined by orthokeratinized squamous epithelium and showing keratinous debris in the lumen and adnexal glands in the wall (H&E × 10)

dermoid cysts in the head and neck region (Pryor [46]) identified 22 months as the median age for presentation. The most common location of dermoid cysts were orbit (61%), neck (18%), scalp and forehead (10%), nasal (6%), and ear (4%).

Macroscopic Features: The average size of the cysts is 1 cm in diameter [46]. They show a smooth external surface and keratinous content.

Microscopic Features: The cysts are lined by keratinized epithelium with adnexal structures in the wall. Figure 15.6.

Differential Diagnosis: Epidermal inclusion cyst, branchial cleft cyst [28].

Cystic and Mature Teratoma

Definition: Neoplasms derived from multipotential cells that contain elements of all three blastodermic layers (ectoderm, endoderm, and mesoderm), with tissues foreign to the site of origin [28]. However, in recent decades, this definition has become less stringent with the acceptance of examples that are composed of bidermal components [47].

Head and neck teratomas account for 2–3% of all pediatric teratomas [47, 48]. In this area, the common sites of origin include the anterior or lateral neck (where the thyroid may be involved), oropharynx (where the tumor may protrude from the mouth), nasopharynx, orbit, and paranasal sinuses [47, 49].

Clinical Presentation: Refer to Chap. 14.

Classification/Subtypes of the Condition: Teratomas are usually histologically benign (although they may lead to death due to severe respiratory compromise). However, they may harbor malignant components and have an aggressive biological behavior.

Macroscopic Features: Cystic or partially solid tumors with a diameter between 3 and 11 cm [28, 47]. The tumor is usually well demarcated, and the solid component may include osseous and/or cartilaginous components.

Microscopic Features: Mature and immature derivative elements of two or three germinal layers are identified. The solid areas may include neutral tissue, pigmented retinal cells, skin and skin adnexal elements, smooth muscle, glands, cartilage, bone, gastric, and pancreatic tissue. In cystic teratomas, epithelial lining is seen covering the inner aspect of the cyst's wall. The tumor should be extensively sampled in order to exclude the presence of malignant elements. Although unusual, malignant extragonadal teratomas have been described [50]. Among malignant extragonadal germ cell tumors, Yolk sac tumor is the leading histologic type, occurring most commonly in association with a teratoma and rarely alone [50]. Figures 15.7a and b.

Differential Diagnosis: This includes salivary gland anlage tumor (see below) and dermoid cysts. Also, nasopharyngeal teratomas with neuroglial tissue and intracranial component need to be differentiated from an encephalocele.

Congenital Fibrosarcoma (CFS)

Definition: CFS is a mesenchymal neoplasia that affects infants and children younger than 2 years of age; they have a relatively good prognosis and rarely metastasizes. CFS characteristically harbors an ETV6-NTRK3 gene fusion in addition to extra copies of chromosomes [51–54]. It represents 5%–10% of sarcomas in this age group [54]. Congenital/infantile fibrosarcoma more commonly involves lower extremities and is not frequent in the head and neck region, corresponding to < 1% of fibrosarcomas [55–57].

Clinical Presentation: Refer to Chap. 14.

Hereditary/Genetic Features: CIF characteristically harbors a chromosomal translocation t(12;15)(p13;q25), which gives rise to an ETV6-NTRK3 gene fusion [51, 52, 58, 59]. Recently, a case of recurrent was found to be negative for the ETV6-NTRK3 translocation but harboring a somatic t(2;15)(2p21;15q25) translocation resulting in the novel fusion of EML4 with NTRK3 [54].

Macroscopic Features: Nonencapsulated tumor with poorly defined margins and a fleshy cut surface.

Microscopic Features: CFS shows moderate cellularity, with round and spindle-shaped cells that adopt a herringbone pattern. The tumor has a primitive appearance and shows scattered inflammatory cells, areas of necrosis, and other showing hemangiopericytoma-like features [52]. Figure 15.8.

Immunohistochemistry/Molecular Diagnostic Features: CFS expresses vimentin. It is negative for pancytokeratin, desmin, smooth muscle actin, MyoD1, CD31, neuron spe-

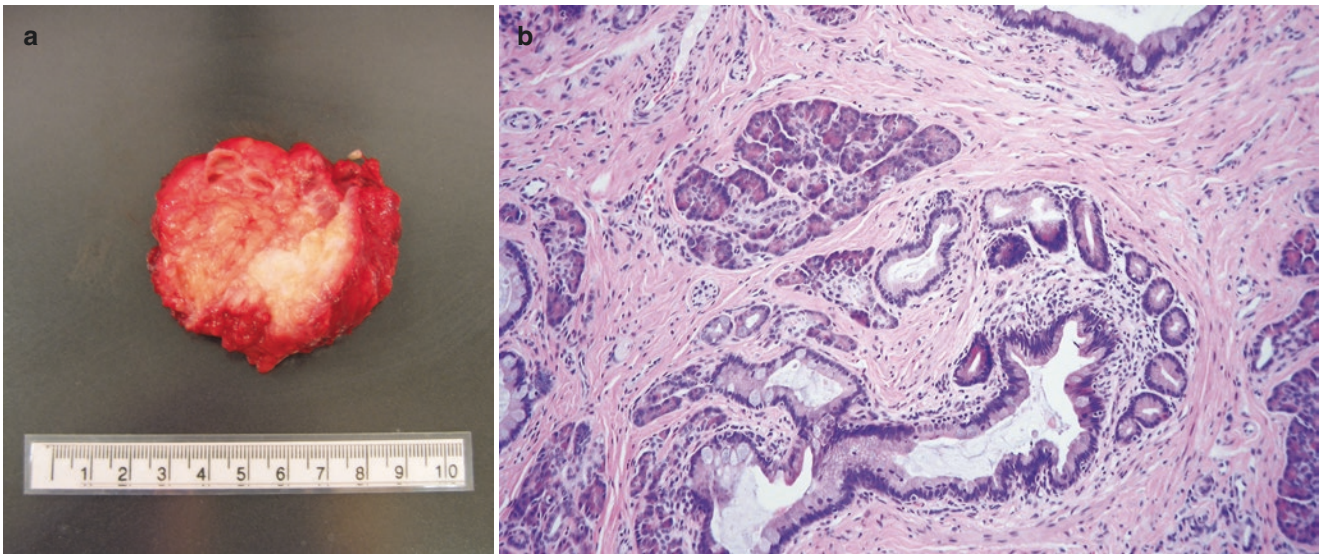

Fig. 15.7 (**a**) Gross appearance of a 6 × 3 cm solid mass in the neck; (**b**) the histology shows colonic and pancreatic derivatives (H&E × 20)

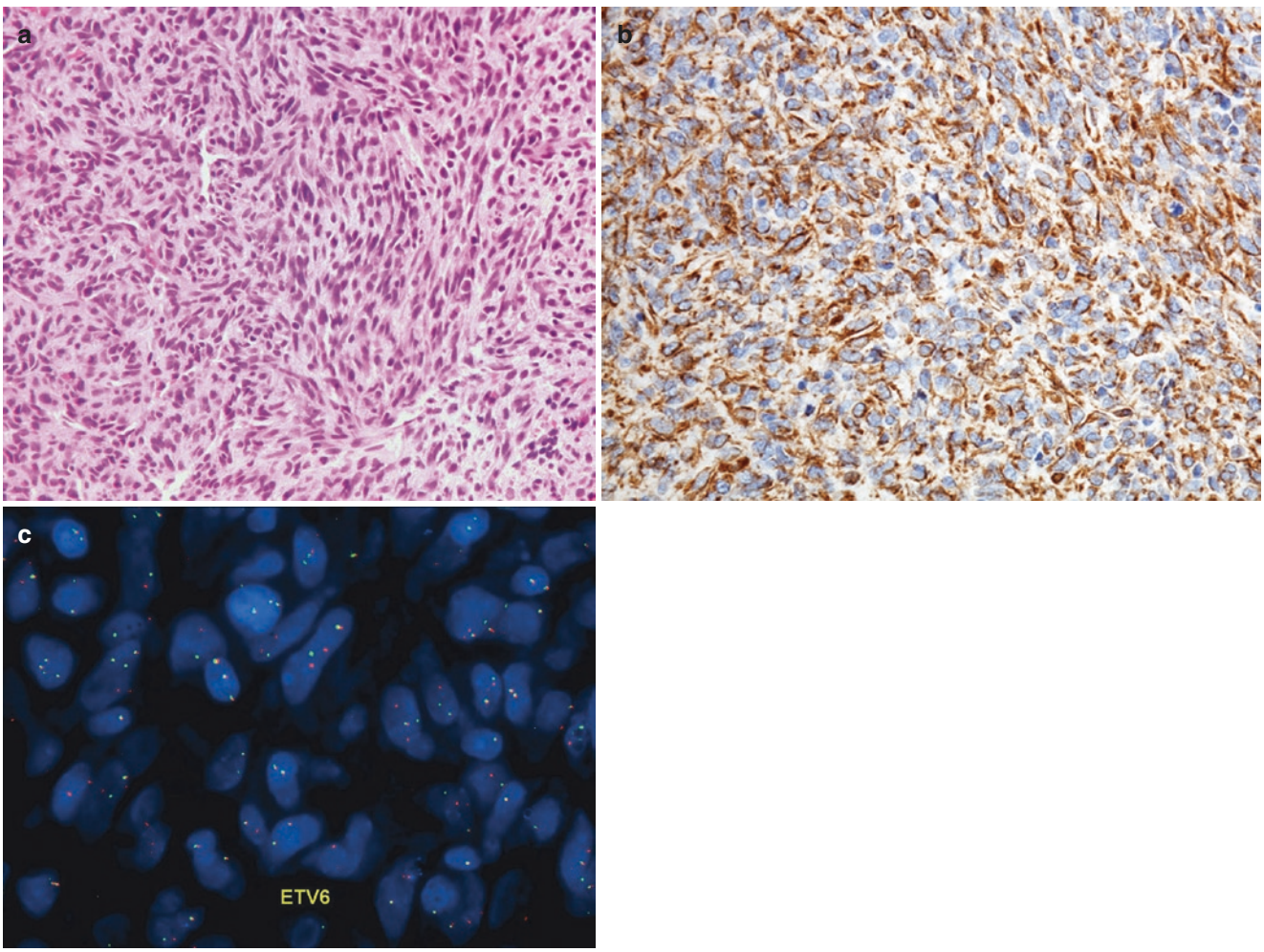

Fig. 15.8 (**a**) Congenital fibrosarcoma with round and spindle-shaped cells, mitotic figures, and scattered inflammatory cells (H&E × 40). (**b**) membranous vimentin expression (Vim immunohistochemistry × 20). (**c**) fluorescence in situ hybridization using break-apart probes demonstrating a translocation of the ETV6

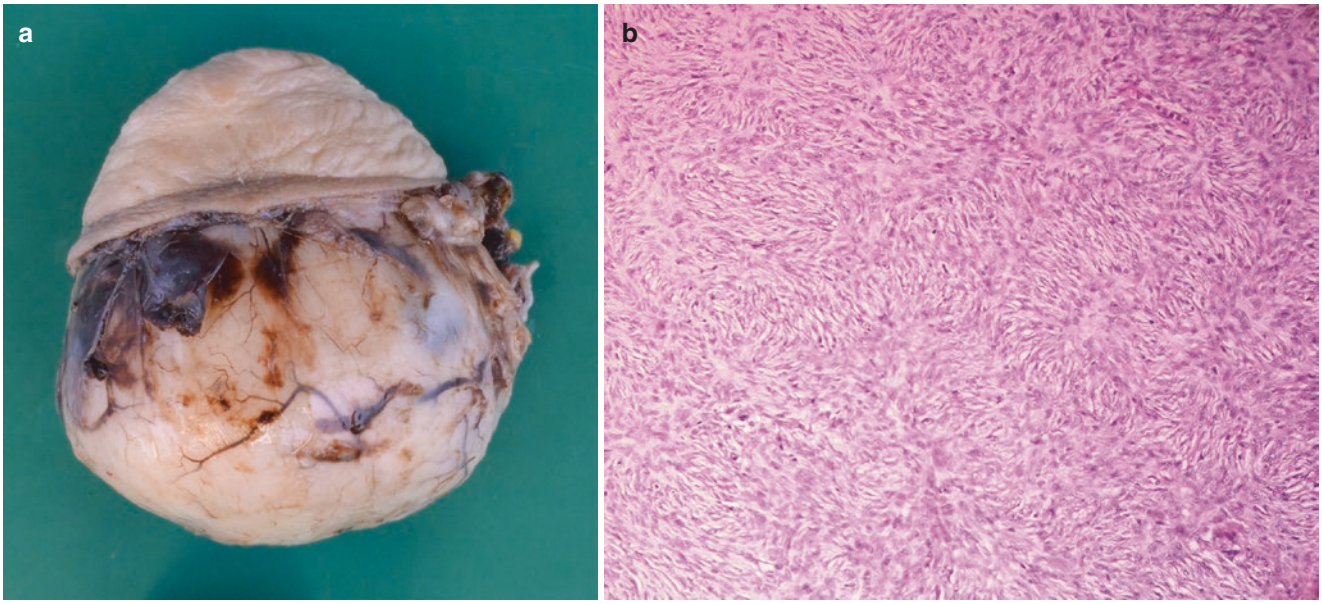

Fig. 15.9 (**a**) Neck nodule measuring 3 cm × 2 cm, covered by normal looking skin. (**b**) the histology shows a spindle cell lesion, with a bland appearance and a herring-bone pattern. COL1A1-PDGFB fusion gene was demonstrated, confirming the diagnosis of dermatofibrosarcoma protuberans

cific enolase, S100, synaptophysin, CD56, and other mesenchymal or epithelial markers [60]. Proliferative index assessed with Ki 67 (MIB-1) is low. Fluorescence in situ hybridization (FISH) using break-apart probes to detect a translocation of the ETV6 and/or NTRK3 genes is routinely used to confirm diagnosis of congenital fibrosarcoma [58]. Figure 15.8c.

Differential Diagnosis: CIF scan mimic vascular lesions and can be clinically masquerade as hemangioma or a vascular malformation [61]. Infantile myofibromatosis, especially in its solitary form, should be considered in the differential diagnosis of CIF [62]. Rare cases of congenital dermatofibrosarcoma protuberans (DFSP) have been described [63, 64]. DFSP is a cutaneous fibrohistiocytic tumor of intermediate malignancy, which presents a COL1A1-PDGFB fusion gene (detected in > 90% of cases) [65]. Figure 15.9a–c.

Rhabdomyomatous Mesenchymal Hamartoma

Definition: Rare congenital rare tumor-like lesion, which occurs in the skin of newborns or infants, principally of the face and neck [66]. Isolated case reports have been described in unusual sites, including oral cavity, vagina, the digit, or the anal region [67–69].

Clinical Presentation: Refer to Chap. 14.

Hereditary/Genetic Features: A proportion of the few rhabdomyomatous mesenchymal hamartomas described associated with a hemangioma [70] or a nasofrontal meningocele and dermoid cyst in the same area [71].

Macroscopic Features: Dome-shaped papule or a polypoid pedunculated lesion ranging from few millimeters to 1–2 cm [72].

Microscopic Features: The tumor presents randomly oriented mature striated muscle tissue with haphazardly associated adipose tissue, blood vessels, pilosebaceous units, and peripheral nerves [66, 69].

Differential Diagnosis: This includes superficial lipomatous nevus, fibrous hamartoma of infancy, neuromuscular choristoma (benign Triton tumor), rhabdomyoma, and cutaneous embryonal rhabdomyosarcoma [72].

Salivary Anlage Tumor

Definition: Hamartomatous tumor arising from the seromucinous glands of the nasal cavity [73].

Clinical Presentation: Nasal airway obstruction in the neonatal period, although the diagnosis may be delayed until 2–3 months of age. Babies may present with respiratory distress, nasal airway obstruction, stridor, and poor feeding. This tumor is more common in male babies and is often attached by a small pedicle to the posterior septum or the posterior nasopharyngeal wall [74].

Macroscopy: Polypoid to pedunculated, well-circumscribed mass with a smooth surface up to 4 cm in maximum dimension with a firm and tan cut section [75].

Cut section may also show a hemorrhagic cystic appearance with gelatinous yellowish material in the cystic foci [74].

Microscopy: The surface is lined by non-keratinizing squamous epithelium with an underlying fibromyxoid stroma composed of spindle cells with variable cellularity. Embedded in this stroma toward the periphery of the lesion, there are squamous islands and duct-like structures, some arising from the surface epithelium [75, 76]. In the center, there are mesenchymal-appearing nodules composed of short fascicles or ovoid to spindle-shaped cells with no atypia. Some nodules are discrete, while others tend to blend into each other [74]. There may be foci of necrosis with cystic degeneration.

Immunohistochemistry: The epithelial structures are positive for cytokeratins and EMA and the solid stromal nodules are positive for vimentin, SMA, and cytokeratin.

Differential Diagnosis: Nasopharyngeal dermoids and teratomas ("hairy polyps") are more frequent in females. Malignant tumors in the neonatal nasopharynx are extremely rare. Heterotopic neuroglial tissue in the neonate has been reported [74].

Congenital Granular Cell Tumor (CGCT)

Definition: Benign tumor of uncertain origin affecting the gingival mucosa of neonates [77]. CGCT has also been described in the literature as congenital epulis, granular cell rhabdomyoma, congenital myoblastoma, or Neumann's tumor [77]. CGST is a rare lesion, with an incidence of just 0.0006% [78].

Clinical Presentation: See Chap. 14.

Hereditary/Genetic Features: CGCT has a higher incidence in females. It is not known an association with congenital anomalies. However, isolated cases have been reported to be associated with neurofibromatosis, polydactyly, binder syndrome, congenital goiter [79], and bilateral transverse facial cleft [80].

Macroscopic Features: Smooth-surfaced, wide-based polypoid nodule, usually single (90%), ranging in size from several millimeters to several centimeters [77]. Tumors measuring up to 9 cm have been described [81].

Microscopic Features: The tumor is well circumscribed and displays nests and ribbons of tightly packed, homogeneous, polygonal to slightly spindled cells with an eosinophilic and granular cytoplasm and single basophilic nucleus (granular cells), scattered amidst connective tissue and fibroblasts. Figure 15.10. The tumor is covered by mucosa lined by squamous epithelium [82]. Occasional CGCT may demonstrate unusual features, such as fibrosis and spindle cell proliferation, which may result during trauma or spontaneous regression of the lesion [82].

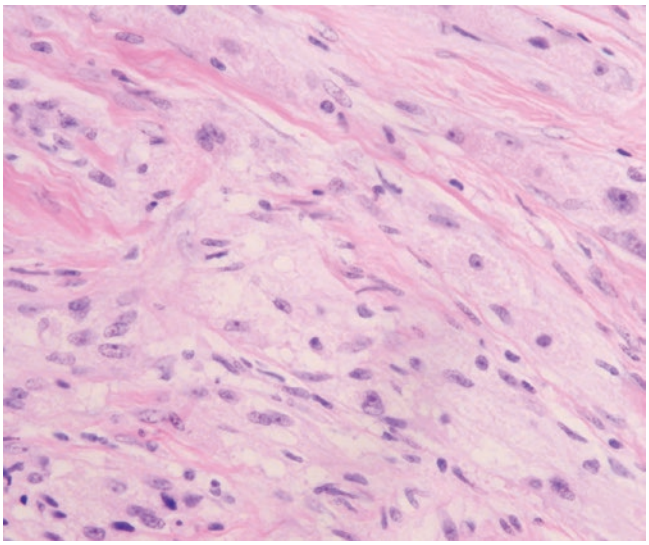

Fig. 15.10 Polygonal cells with an eosinophilic and granular cytoplasm and single basophilic nucleus in a congenital granular cell tumor (H&E × 20)

Immunohistochemistry Features: CGCT expresses vimentin and neuron-specific enolase [82]. It is characteristically negative for S100 protein, NGFR/p75, and inhibin-alpha, which helps differential diagnosis with the adult type granular cell tumor, which affects internal organs, is of neural origin, and not congenital [51, 83]. CGCT also lacks immunoreactivity for CD31, CD34, CD68, laminin, chromogranin, keratins, desmin, calponin, and smooth muscle actin [82].

Differential Diagnosis: This includes melanotic neuroectodermal tumor of infancy, hemangioma, fibroma, embryonal rhabdomyosarcoma, granuloma, malignant granular cell myoblastoma (adult type granular cell tumor), chondrogenic, osteogenic sarcoma, and schwannoma [83, 84].

Anomalies of the Skin with Histopathlogical Relevance

Cutis Hyperelastic (Ehlers-Danlos Syndrome-EDS)

Definition: Hereditary disorder of the connective tissue, characterized by hyperextensible skin, joint hypermobility; and varying degrees of vessel and tissue fragility [85].

Clinical Presentation: See Chap. 14.

Hereditary/Genetic Features: EDS types I, II, and III are the most common forms, with an autosomal dominant mode of inheritance. Specific mutations in pro-alpha-1 collagen chains have been described for EDS I and II. Instead, type III has more than one mutations involved [86]. The other less frequent types of EDS can have an autosomal dominant or recessive trait.

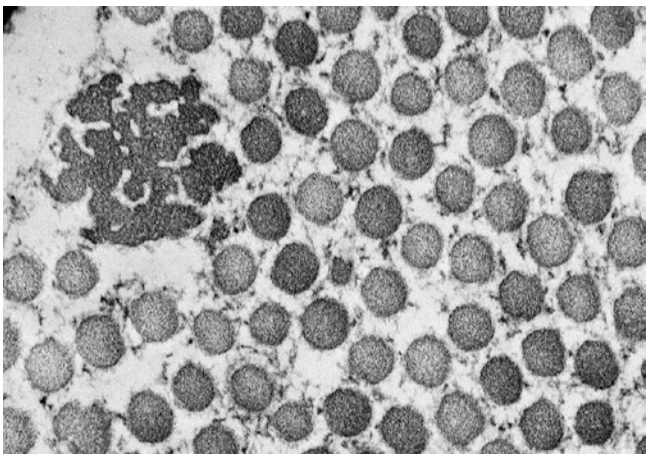

Fig. 15.11 Four year-old patient presenting with atrophic scars and hypermobile joints typical of classical Ehlers-Danlos syndrome. The electron microscopy shows numerous fibrous collagen fibrils (up to 450 nm diameter) present in transverse sectional orientation (also known as collagen flowers or spiral collagen). (Magnification 20,000x). Photo kindly provided by Bart E Wagner, Chief BMS. Sheffield Teaching Hospitals. UK

Classification/Subtypes: Based on the clinical presentation and genetic features, Ehlers-Danlos syndrome has been classified in more than 10 subtypes. The main forms are classical, hypermobile, vascular, kyphoscoliotic A/B, arthrochalasis A/B, and dermatosparaxis types.

Macroscopic Features: Not relevant.

Microscopic Features: The skin may be normal or show dermal thinning (most common in type IV). Electron microscopy is helpful to demonstrate abnormalities in the collagen bundles. Figure 15.11.

Multiple Lentigines (Leopard Syndrome)

Definition: Rare syndrome characterized by the presence of L: lentigines, E: electrocardiographic conduction defects, O: ocular hypertelorism; P: pulmonary stenosis; A: abnormalities of the genitalia; R: retardation of growth, and D: deafness. Not all these manifestations are present in every case [87].

Clinical Presentation: See Chap. 14.

Hereditary Features: Familial incidence with a dominant trait.

Macroscopic Features: Dark-brown skin flat macules.

Microscopic Features: Moderate elongation of rete ridges of the skin with increased number of melanocytes in the basal cell layer and an increase amount of melanin in both the melanocytes and the basal keratinocytes, and melanophages in the upper dermis [87].

Differential Diagnosis: Mainly with Peutz-Jeghers syndrome, lentiginosis profuse, speckled lentiginous nevus, and Carney complex.

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