8 Clinical and Surgical Management of Pediatric Diseases of the Nasopharynx and Sella Turcica

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Benign Tumors and Cysts

Thornwaldt Cyst

Definition

Thornwaldt cyst (a.k.a Tornwaldt cyst and Thornwald cyst) is the second most common epithelial growth in the nasopharynx (second to adenoid hypertrophy) and the most common benign midline cyst in the nasopharynx. This lesion develops in cleavage planes during the pharyngeal and nasal embryogenesis process. The retraction of the notochord results in contact with the endoderm of the embryonal pharynx. The closure leads to the development of the cyst. Respiratory epithelium lines the cyst walls. These epithelial linings accumulate fluid with the cyst [1, 2].

The cyst is often found incidentally on either radiological imaging or nasopharyngeal examination. The peak incidence ranges between 15 years and 60 years of age. This is likely due to the gradual accumulation of fluid. The prevalence of Thornwaldt cysts at autopsy is 4%, whereas the incidence in radiological images is approximately 0.06% [2, 3].

Presentation

These lesions are almost always asymptomatic. Some patients may present with post nasal drip, if the cyst bursts, halitosis, or periodic discharge if it gets infected. In rare occasions, otitis media with effusion may result if the cyst is large enough to cause Eustachian tube obstruction. Some refer to a symptomatic cyst as Thornwaldt disease [1, 3].

On physical examination, these cysts present as midline nasopharyngeal lesions that are cystic, and with smooth overlying mucosa. These cysts often have a yellow hue, but they present with darker color due to hemorrhage or hemosiderin content [1, 3].

Differential Diagnosis

Several nasopharyngeal masses can present with cystic components. As such, the differential diagnosis of the Thornwaldt cyst includes:

1. Adenoid hypertrophy.
2. Rathke's cleft cyst.
3. Mucous retention cysts.
4. Meningocele.
5. Neurenteric cysts.
6. Minor salivary gland tumors.
7. Nasopharyngeal carcinoma.

Radiological Features

These cysts have a classical characteristic appearance on radiological imaging. They are typically round, well-circumscribed lesions just deep to the mucosa. They reside anterior to the longus colli muscles and project the overlying mucosal surface into the nasopharynx.

On CT scan, their appearance is of low-density nonenhancing cysts, though they may present as a hyperattenuated lesion if the fluid is rich in protein. On magnetic resonance imaging (MRI), they demonstrate a classic cystic appearance. T1 sequence is variable depending on the protein content; T2 is high, without any enhancement on T1 with gadolinium [2, 4].

Management

If the lesion is asymptomatic, it does not require any treatment. If the lesion has darker contents, it should be biopsied after adequate imaging has been performed to rule out mucosal melanoma. If deemed necessary, the cyst can be marsupialized or completely excised endoscopically through a transnasal approach. Similarly to adenoidectomy, the wound heals well after surgery [1, 3].

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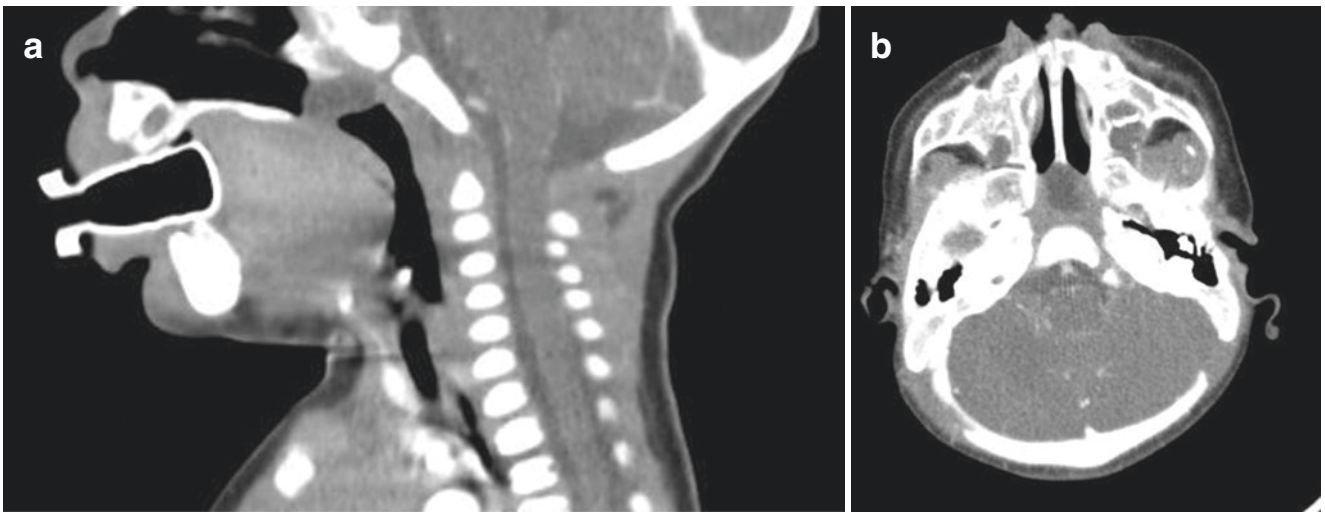

Fig. 8.1 (**a**) Sagittal CT scan shows a nonenhancing mass in the posterior nasopharyngeal wall. (**b**) Axial CT scan shows a nonenhancing mass in the posterior nasopharyngeal wall

Case Presentation

A 7-week-old male presented with a history of stertorous breathing since birth. The breathing worsened and feeding was challenging. This resulted in repeated visits to the emergency department. Flexible nasal endoscopy revealed a large nasopharyngeal mass and arytenoid edema. A CT scan revealed a nonenhancing mass in the posterior nasopharyngeal wall (Fig. 8.1a and b). The mass was excised through a transoral/adenoidectomy approach (Figs. 8.2, 8.3 and 8.4).

Rathke's Cleft Cyst

Definition

Goldziehler was the first to describe the Rathke's cleft cysts (RCC) in 1913 as a postmortem finding. RCCs are epithelial intrasellar cysts that develop from Rathke's pouch remnant. They are often round or dumbbell shaped [5].

RCC are found in ~15% of autopsies. There is a female predominance of 2:1 [5].

Rathke's pouch develops as a diverticulum from the stomodaeum on the 24th day of embryonic life. At the same time, the neuroepithelium forms with the down growth forming the infundibulum. The pouch occludes at the level of the buccopharyngeal junction. On the sixth week of gestation, Rathke's pouch and the oral epithelium separate, and the pituitary gland pars distalis develops. At this point, the residual lumen usually regresses. If it persists, it is then considered an RCC [5–7].

The cyst wall is often lined with ciliated columnar epithelium containing goblet cells (see Chap. 7). Desquamated cellular debris forms the solid component of the intraluminal nodule of the cyst [6–9].

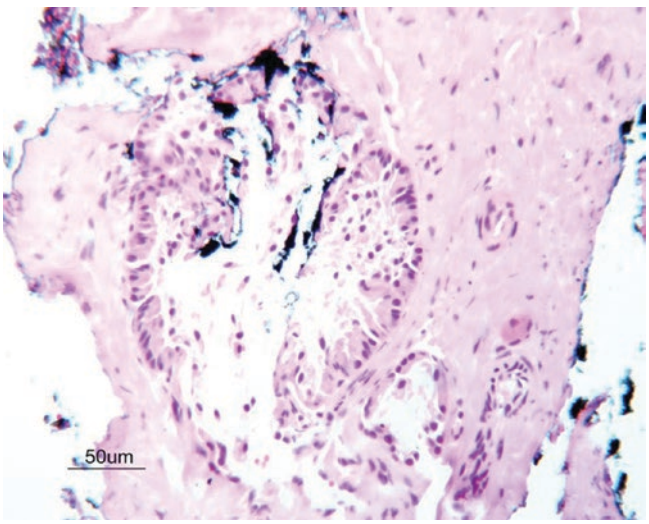

Fig. 8.2 The presence of an epithelial cell-lined cyst is identified within lymphoid tissue and pharyngeal tissue

Clinical Presentation

The majority of RCCs are asymptomatic and are discovered incidentally. Usually they are less than 2 cm in size. When they are symptomatic, the symptoms are often secondary to compression of surrounding structures. Pituitary dysfunction can result from pressure on the pituitary gland, whereas visual disturbance (e.g., bitemporal hemianopia, optic atrophy, reduction of visual acuity, and chiasmatic syndrome) may result from pressure on the optic chiasm. In a study by Rao and colleagues, visual disturbance was the most common presenting symptom. In another study by Voelker et al., pituitary dysfunction was more prevalent. They also demonstrated that visual field defects was the second most common presenting symptom [7–10].

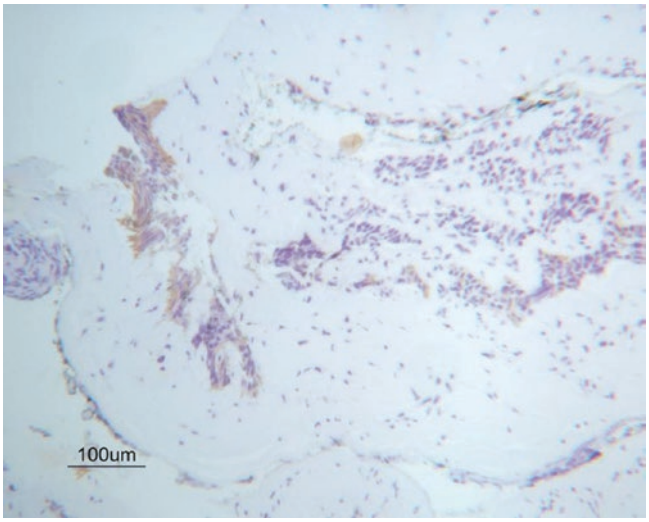

Fig. 8.3 The epithelial cells shown in Fig. 8.2 are positive for cytokeratin immunostain

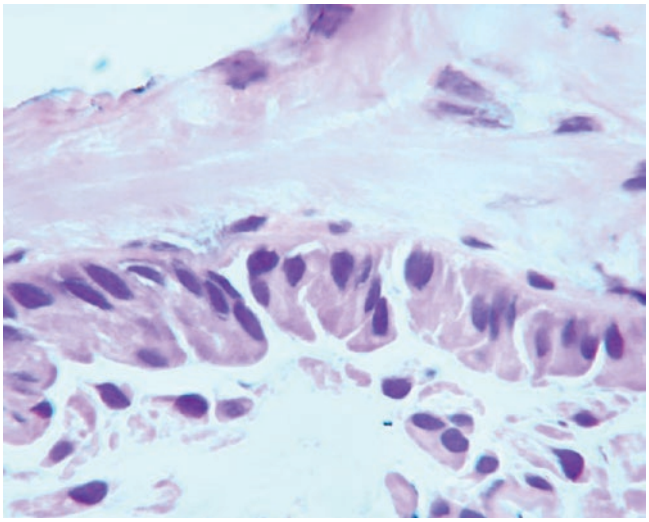

Fig. 8.4 The lining cells at high magnification show features of a ciliated columnar epithelium

Shin et al. reported that impotence and low libido were the most common presenting symptoms in men, while in women, hyperprolactinemia was prevalent.

Pituitary apoplexy, giant cysts, hypophysitis, aseptic meningitis, sphenoid sinusitis, intracystic abscess, and empty sella syndrome are all rare but documented consequences of RCC [7–10].

Differential Diagnosis

The main differential diagnosis for RCC includes the following:

1. Pituitary adenoma.
2. Craniopharyngioma.
3. Arachnoid cysts.
4. Epidermoid cysts.
5. Teratoma.

Radiological Features

RCC can be seen in radiological testing as a well-defined midline cyst that does not enhance. The cyst arises within the sella coming out of the anterior and intermediate lobes of the pituitary. Up to 60% of RCC have a suprasellar extension.

On CT scan, RCC appear as a hypoattenuating well-circumscribed cystic sellar mass, but it can also appear as isoattenuating or hyperattenuating depending on the cystic contents. With contrast, the cyst is classically nonenhancing, but in some cases, the cyst wall may enhance. Due to these variabilities, CT scan findings alone cannot support a definitive diagnosis of RCC. On CT scan, a simple RCC cannot be distinguished from an epidermoid or an arachnoid cysts, whereas more complex cysts cannot be distinguished from pituitary adenomas and craniopharyngiomas.

Similarly, MRI findings of RCC can be highly variable. This is due to the variability of the cyst composition, which can be mucoid or serous. Thus, there are no classic MRI features of RCC, though many RCC will be either low signal intensity on T1 sequence and high intensity on T2 or high intensity on T1 and variable intensity on T2. With gadolinium, there is no increased uptake in the cyst, but the compressed pituitary tissue will be more visible [11, 12].

The only pathognomonic sign of RCC is a small nonenhancing intracystic nodule. This sign is not present in all cases. Sometimes, a fluid level can be seen as well.

With angiography, the main abnormality seen is the avascular mass effect with elevation of the anterior cerebral arteries, namely, the A1 segment [11, 12].

Management

The treatment for symptomatic RCC is surgical resection. With the advances in endoscopic skull base surgeries, the most acceptable contemporary approach is endoscopic transphenoidal surgery, in which the cyst is either excised or drained. Radical excision is often not needed and avoided due to the increased risk of pituitary injury [13–15].

There are two main approach endoscopically, either transethmoid–transsphenoidal or transnasal/septal–transphenoidal. In the former, the surgeon would approach the sphenoid through the ethmoid cells by performing a wide ethmoidectomy prior to opening the sphenoid sinus. The transnasal/septal approach does not involve dissecting the ethmoid cells, rather approaching the sphenoid sinus through the natural ostium and performing a postrosuperior septectomy. The advantage of the latter approach that its faster, where the former can provide a wider exposure and is safer in patient with altered or challenging sinus and nasal anatomy [13–16].

After the excising the intersinus septum of the sphenoid and exposure of the cyst made, the cyst is then opened and biopsy is obtained from the cyst wall. After marsupializing the cyst wall, and opening it to drain into the sphenoid the surgery can be concluded unless there is a cerebrospinal fluid (CSF) leak. If present, a previously harvested nasal septal flap can be used for reconstruction along with fat and fascia lata. In patients where the cyst is not accessible with an endoscopic approach, a craniotomy may be necessary.

Postoperatively, most patients show improvement in their symptoms and resolution of the RCC. The greatest improvement is mostly noted on the neurogenic and ophthalmologic symptoms. More than half of the patients with amenorrhea, galactorrhea, and/or oligomenorrhea show improvement as well [13–15].

Similarly to other skull base surgical cases, the most common surgical complications include CSF leak, diabetes insipidus, and meningitis. Abscess formation in the cyst location was reported in literature as well. Recurrence rate is higher with craniotomy compared to endoscopic approaches. In cases with recurrence, comprehensive cyst wall removal is indicated, with some advocating for external beam radiation postoperatively, although the benefit of the radiation and its role is not well established [13–15].

Adenoid Hypertrophy

Definition (Classification/Subtypes, Epidemiology, Genetics, Etc.)

Adenoid disease usually presents with either infectious process or obstructive symptoms, namely, sleep disordered breathing. Currently, the most common indication for adenoidectomy (or adenotonsillectomy) is sleep-disordered breathing (SDB) [17]. This shift from recurrently infections is due to the evolution in treatment of infections, in addition to further recognition of the health impact of SDB on children [17–19].

The most recent data indicate that over half a million adenotonsillectomy are performed annually in the USA making adenotonsillectomy the second most common procedure performed in children.

Tonsils and adenoids are lymphoid tissues that originate from the surface epithelium of the mesenchymal stroma. Adenoids, known also as pharyngeal tonsils, are located in the posterior surface of the nasopharynx in close proximity to the mucous glands. Alongside the palatine tonsils (often referred to as tonsils) and lingual tonsils, they form the Waldeyer's Ring. The lining of the adenoids is pseudostratified ciliated columnar epithelium. The development of the adenoids is by the fusion of two lateral primordial at the midline during the seventh month of gestation. It continues to grow until the fifth year of life. Afterwards, it tends to gradually regress. Coupled with the growth of the nasopharynx, the airway passage improves. The adenoids are supplied by the ascending pharyngeal artery, the pharyngeal branch of the maxillary artery, the ascending palatine artery, the artery of the Pterygoid canal, and tonsillar branch of the facial artery. The venous drainage lands to the internal jugular vein through the pharyngeal plexus. Lymph drainage is through the retropharyngeal and pharyngomaxillary lymph nodes [17–19].

Adenoids are B-cell organs predominantly. There is evidence that the adenoids, alongside the tonsils, are part of the secretory immunity and the regulation of secretory immunoglobulins. The adenoid produces IgA, IgG, IgM, and IgD. The adenoid is located in preferable location to mediate immunity in the upper aerodigestive tract [20–24].

Clinically, physicians and surgeons tend to distinguish between adenoiditis and adenoid hypertrophy, though; most of the adenoid hypertrophy is due to chronic or mild infections of the adenoid.

The most common viruses to cause adenoiditis fall under the umbrella of "common cold." These viruses are rhinovirus, adenovirus, influenza virus, parainfluenza virus, reovirus, coxsackievirus, echovirus, and respiratory syncytial virus. However, Stept. pneumonia, H. influenza, group A streptococcus, and Moraxella catarrhalis are the most common to cause bacterial adenoiditis [20–24].

The normal flora of the upper airway consists of actinomyces, fusobacterium, nocardia, bacteroides, leptotrichia, and propionibacterium. A child usually establishes this normal flora gradually before the age of 5 years [17, 20, 21, 23].

As mentioned earlier, chronic or recurrent adenoiditis play a role in adenoid hypertrophy. Some studies have shown a correlation between bacterial load on the tissue and the number of lymphocytes. Despite the chronic infections theory, when patients present with adenoid hypertrophy, antibiotics are often not indicated [17, 20, 21, 23].

Clinical Presentation

The most common presenting symptoms of adenoid hypertrophy are snoring, mouth breathing, and hyponasal speech. Other nonspecific symptoms include chronic cough, rhinorrhea, and postnasal drip. These children can also present with adenoid facies.

Hyponasal assessment can be accomplished by asking the patient to repeat phrases or words that emphasize nasal emission. Phonemes with such charters are "m," "n," or "ng."

Palatal evaluation is necessary for all patients being considered for an adenoidectomy. Submucous cleft of the soft palate is often missed and can result in velopharyngeal deficiency (VPD) postoperatively. Furthermore, children with neuromuscular anomalies are at a higher risk of developing VPD postoperative.

Middle ear effusion (MEE) can be caused by enlarged adenoids that are obstructive to the Eustachian tube. Children who have recurrence of MEE after a set of pressure equalizing tube (PET) should be evaluated for adenoid hypertrophy [17–19, 24].

Chronic rhinosinusitis (CRS) in children that does not respond to medical therapy may be caused by chronic adenoiditis or an adenoid that is functioning as a reservoir for biofilms and bacteria. For these patients, performing an adenoidectomy is usually helpful in avoiding a more aggressive sinus surgery.

In children, obstructive sleep apnea (OSA) or generally SDB is mainly caused by enlarged adenoids and tonsils. Often the problem only resides in the enlarged adenoids. The parents would complain about continued mouth breathing, snoring, and witnessed apneas. Other symptoms include nocturnal neck extension, enuresis, restless sleep, drooling, night terrors, and sleepwalking. Children with SDB can have daytime sleepiness, attention deficit disorders, headaches (especially in the morning), dry mouth, halitosis, and behavioral changes. These children need to get thoroughly investigated. Assessment of the size of the adenoids should be performed with either nasopharyngoscopy or lateral neck X-ray, which the former being more specific. The adenoid is then sized according to the percentage of blockage to the nasopharynx: 0%, 25%, 50%, or 100%. If a severe OSA is suspected, a sleep study is recommended prior to surgical intervention. Polysomnography (PSG) is the gold standard in diagnosis and assessing OSA. Mild OSA is considered when apnea hypopnea index (AHI) is more than 1 but less than 5, moderate OSA is AHI 5–10, and severe OSA when AHI > 10 [17–19, 24].

Overnight sleep oximetry is a cheaper and more readily available test that can help screen patients for OSA. The McGill Oximetry score (MOS) is used to define severity, with MOS 4 being the most severe, and MOS 1 representing normal exam or inconclusive [25, 26].

Differential Diagnosis

Adenoid hypertrophy is a clinical diagnosis. The differential diagnosis in a typical case is limited, though other disease can present with a nasopharyngeal mass, including lymphoma and nasopharyngeal carcinoma.

Radiological Features

When the children are cooperative, a simple nasopharyngoscopy is usually sufficient in diagnosing and evaluating the nasopharynx for adenoid hypertrophy, though when indicated, plain lateral X-ray is the main imaging study required. While assessing a lateral neck X-ray, the physician should look at degree of nasopharyngeal airway narrowing.

If there is a suspicion of a tumorous process in the nasopharynx or the diagnosis is not clear, a CT scan or an MRI is indicated to further assess the extent and nature of the tissue. Furthermore, in children with CRS, CT scan is indicated to assess the sinuses.

Management

After ruling out severe OSA, a trial of medical treatment can be considered. This includes saline nasal sprays and nasal corticosteroid sprays (NCS). It is controversial whether the nasal corticosteroid is able to reduce the size of the adenoid. Some studies reported improvement on NCS with rebound worsening when the NCS was stopped.

Adenoidectomy is indicated if adenoid hypertrophy is associated with excessive snoring and mouth breathing or OSA and sleep disturbance. If SDB is not well documented, but the child has an obstructive adenoid with either cor pulmonale, failure to thrive, dysphagia, speech abnormality, craniofacial growth abnormalities, occlusion abnormalities, or speech abnormalities, an adenoidectomy is indicated to avoid long-term sequelae. Other indications for an adenoidectomy include recurrent/chronic MEE, recurrent/chronic acute otitis media (AOM), CRS, and if the adenoids are suspicious for malignancy.

There are several different techniques in performing an adenoidectomy. The most widely used is the curette (cold instruments technique). It involves using various sizes of curettes to scrape off the adenoids from the nasopharynx. Suction cautery technique involves fulgurating and suctioning the adenoid. This technique is fast and produces less bleeding compared to cold instruments technique. Recently, some surgeons have been using the microdebrider. In a study performed by Koltai et al., this technique was found to be faster, less bleeding, and had a higher satisfaction rate from the surgeons when compared to cold instruments technique.

Most adenoidectomy can be performed in an outpatient basis safely. If combined with tonsillectomy, younger than 3 years old patients should spend the night in the hospital postoperatively for observation. This group of patients has been shown to have higher risks of complications, namely, airway complications, compared to older children. Other patients requiring admission are those with history of bleeding disorders, severe OSA, underlying craniofacial anomalies, and/or systemic disorders.

Complications postadenoidectomy is rare, especially when performed without tonsillectomy. Postoperative hemorrhage when it happens tends to be mild and usually responds to nasal decongestant drops. Rarely, nasal packing and surgery is necessary to control the bleeding. VPD is unusual to happen in patients after adenoidectomy. It is more associated with removal of large tonsils. Nevertheless, an unrecognized submucosal cleft of the soft palate can result in a VPD post adenoidectomy [27].

Grisel's syndrome is a rare complication that results from atlantoaxial subluxation of the cervical spine. These patients

have laxity of the anterior transverse ligament and decalcification of the anterior arch of the atlas. The patient ends up complaining from neck stiffness and sternocleidomastoid muscle spasm. The child would hold his head tilted to one side with a mild rotation to the other side. Imaging is necessary to confirm Grisel's syndrome and also rule out retropharyngeal abscess. Intravenous antibiotics and cervical stabilization are used to treat this condition. If an abscess is present, draining is indicated [28].

Nasopharyngeal stenosis is an extremely rare complication and a complicated one to manage. This results from extensive circumferential damage to the nasopharyngeal mucosa. Performing the surgery during an acute pharyngitis phase increases the risk. There are many surgical techniques described to repair the stenosis. Some involve performing a local flap, putting skin grafts, and placing a stent. These techniques have variable success rate and should be tailored according to each patient's specific condition.

If the patient suffers from OSA, the child should get postoperative pulmonary edema. This will manifest with reduced oxygen saturation, pink frothy sputum, and infiltrates in the chest X-ray. If present, fluid restriction and diuresis is indicated, and positive airway ventilation may be needed in severe cases [29].

Case Presentation

A 5-year-old female was referred with persistent nasal obstruction 1 month post adenoidectomy. The nasal endoscopy and CT scan revealed significant rapid regrowth of the adenoid tissue (Fig. 8.5). The adenoidectomy was repeated and the tissue sent for pathological assessment. The pathology revealed a diagnosis of lymphoma.

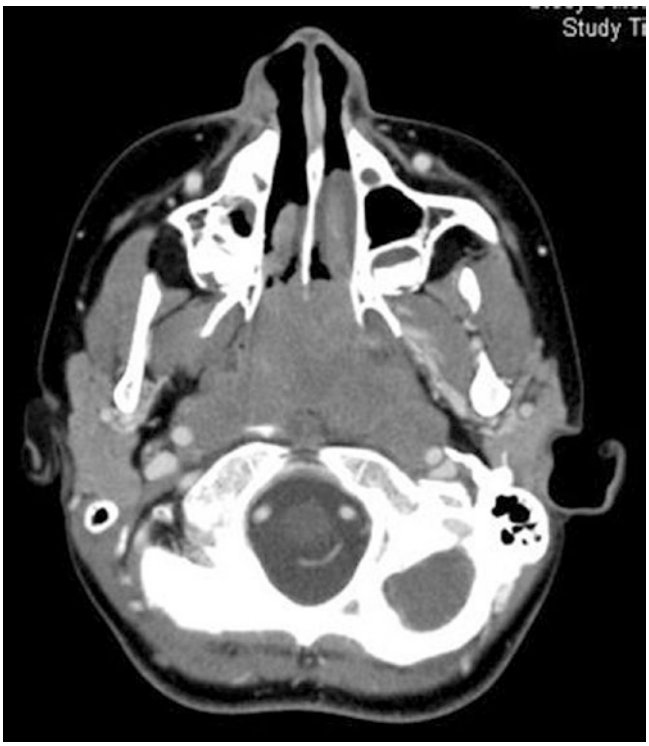

Fig. 8.5 Axial CT shows complete obstruction of nasopharynx in child with "adenoid regrowth" following adenoidectomy. Pathology showed lymphoma

Nasopharyngeal Teratoma

Definition (Classification/Subtypes, Epidemiology, Genetics, Etc.)

Teratomas develop in early childhood and infancy they are generally extragonadal. Teratomas occurring later in childhood are often gonadal. They are the most common pediatric germ cell tumors, 5% of which occur in the head and neck region. They are almost always benign in nature. The incidence of head and neck teratomas is 1 in 40,000 live births and the most common locations are neck, nasopharynx, orbit, and brain [30].

Clinical Presentation

Teratomas present as a mass in the nasopharynx that often protrude to the oropharynx and oral cavity. Small lesions can cause feeding difficulty, but large Teratomas can cause airway compromise. Hence, newborns with teratomas can have respiratory distress that may require intubation or tracheostomy. They can either be pedunculated over a stalk or have a sessile base. Many of these children have other coanomalies, namely, palatal fissures, anencephaly, and hemicranias [30].

Differential Diagnosis

1. Adenoid.
2. Dermoid.
3. Lymphatic malformation.

Radiological Features

Nowadays, Teratomas are most often diagnosed in utero. Classically, maternal polyhydramnios and elevated alpha fetoprotein levels. If the lesion is large enough, it can be detected in the prenatal ultrasounds. The advantage of early detection is to plan an EXIT procedure (ex utero intrapartum treatment) to secure the airway. On prenatal ultrasounds, in addition to polyhydramnios, the fetal head could appear extended and turned toward the side of the lesion due to mass effect.

If the lesion is detected after birth, a CT and an MRI are useful to confirm the diagnosis.

The MRI would allow improved delineation of the lesion, especially in complex tumors. Teratomas are classi-

cally heterogeneous on both T1 and T2 sequences. The mass has cystic tissue and fat. More than half of teratomas have calcifications in them. This is pathognomonic for Teratoma [30].

Management

The treatment of nasopharyngeal teratoma is surgical excision. When they are too large, a transoral approach is usually used with or without endoscopic assistance. Depending on the size of the teratoma, splitting the soft palate for access, or performing a lateral rhinotomy or transcervical approaches may be needed. Rarely, teratomas may have intracranial extension, if present, neurosurgical consultation is necessary and a craniofacial approach would often be the best surgical approach.

Teratomas in general have good outcome. Postoperatively, alpha-fetoprotein is measured periodically to screen for recurrence [30, 31].

Hairy Polyp

Definition (Classification/Subtypes, Epidemiology, Genetics, Etc.)

Hairy Polyps were first described in the late 1800s as rare developmental anomalies. Many regard Hairy Polyps as benign dermoid development that contains both ectoderm and mesoderm cells that are foreign to the location the lesion is at. Another theory has been proposed by Lansford et al. that differentiates between dermoids and hairy polyps, identifying hairy polyps as a branchial arch malformation. This theory is based on the fact that hairy polyps arise from the pharyngeal surface of the first and second branchial arches and that patients with hairy polyps tend to have other features of first and second branchial arches malformations. To date, more than 150 cases of pharyngeal hair polyps have been described in the literature. Females are six times more susceptible to develop them, but there is no indication of a familial incidence. They can arise in many locations, most commonly nasopharynx and oropharynx. Other pharyngeal sites include soft palate, lateral pharyngeal walls, and rarely from the Eustachian tube.

Hairy polyps are not associated with skull base defects, and malignant transformation has not been reported [32–34].

Clinical Presentation

The presentation is usually early after birth. The neonate would present with respiratory distress and stertor. The patient may also have cyanosis, coughing, gagging, and feeding difficulties. These symptoms are likely related to the ball valve effect on the larynx and the prolapse of the lesion into the upper esophagus. If large enough, it can cause total or subtotal airway obstruction leading to the need for intubation or tracheostomy as death has been reported due to hairy polyp obstructing the airway.

Other milder presentation includes snoring, obstructive sleep apnea symptoms, and rarely VPD [32–34].

Differential Diagnosis

The differential diagnosis of nasopharyngeal hairy polyp includes masses of the nasopharynx both cystic and solid

1. Adenoid hypertrophy.
2. Teratoma.
3. Thornwaldt cyst.
4. Rathke's cyst.
5. Hamartomas.
6. Hemangioma.
7. Meningeoenchephaloceles.
8. Lymphatic malformation.
9. Minor salivary gland tumors.

Radiological Features

Imaging is required to diagnose hairy polyps. MRI tends to be more useful than CT scans in these occasions to determine the soft tissue nature and to understand the extent of the lesion. On T1 weighted sequences, fat contents of the hairy polyp produce high signal intensity. T2 weighted sequences are variable intensity. CT scan would demonstrate low density mass. Typically, hairy polyps do not have intracranial extension [33, 34].

Management

Size and the location of the hairy polyp would determine the urgency of the surgical intervention. Hairy polyps are classically pedunculated over a thin stalk. After securing the airway, excising the base with a small margin is usually curable. The best approach usually involves an endoscopic assistant transoral exposure. Complications postoperative are very rare, with mild bleeding being the most common of them. Recurrence is extremely rare as well [33, 34].

Case Presentation

A 1-day-old term infant was assessed in the neonatal intensive care unit with tachypnea, gagging, and cyanosis with feeds. Intra-oral examination revealed an oropharyngeal mass (Fig. 8.6). The 2 cm lesion was pedunculated on a narrow stalk adjacent to the Eustachian tube opening in the nasopharynx (Fig. 8.7). It was excised via a transoral approach using a polyp snare.

The histopathology revealed the following (Figs. 8.8, 8.9 and 8.10):

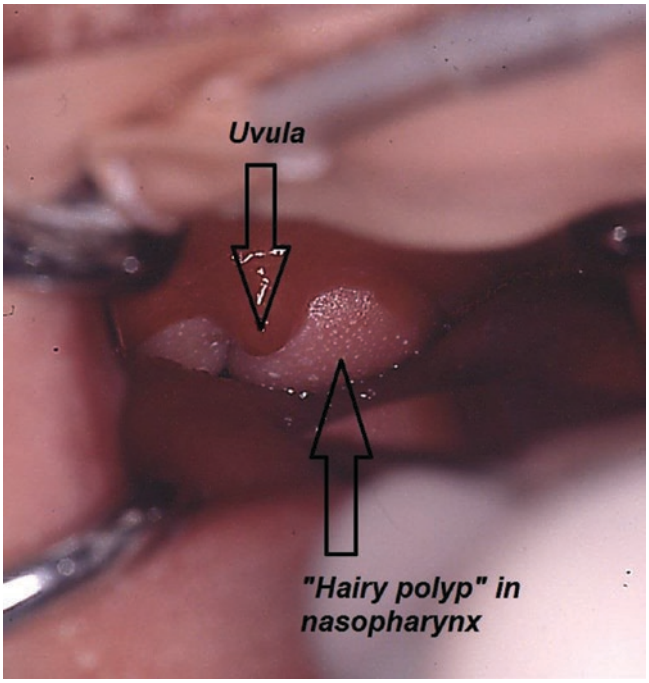

Fig. 8.6 Peroral view shows a thick lined smooth mass filling the nasopharynx with visible hair follicles on the surface

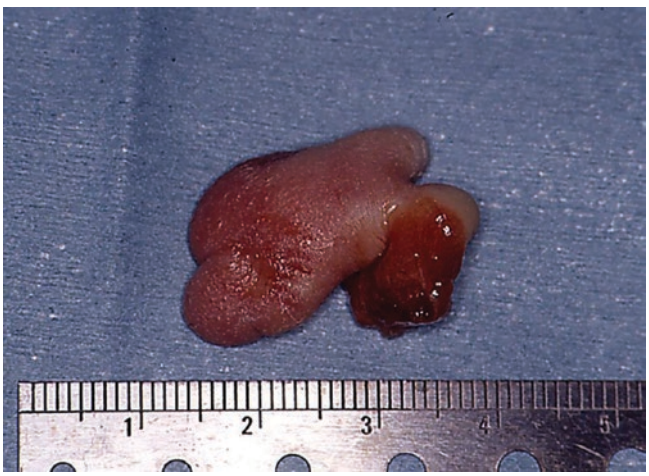

Fig. 8.7 Gross appearance of the mass following excision with snare technique under direct visualization. There is a thick epithelial cover with grossly visible fine hair (see also Chap. 7)

Juvenile Nasopharyngeal Angiofibroma

Definition (Classification/Subtypes, Epidemiology, Genetics, Etc.)

Juvenile nasopharyngeal angiofibromas (JNAs) are rare nasal/nasopharyngeal tumors. They account for less than 0.5% of all tumors in the head and neck. JNA is a fibrovascular tumor with an incidence of 1:150,000. It predominantly affects males in the age range of 14–25 years. There have been reported cases of older men and adolescent girls. JNA

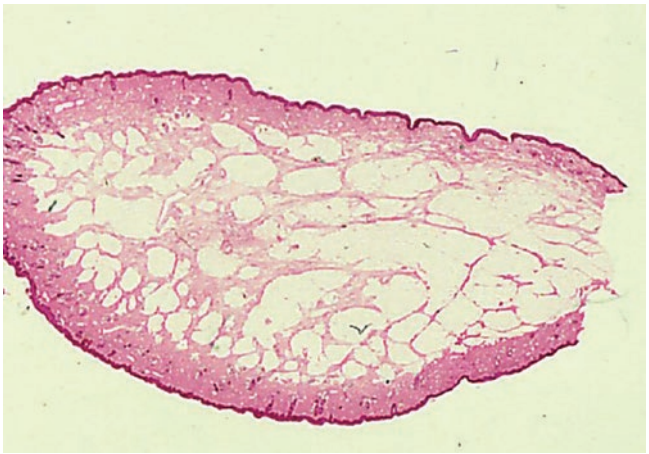

Fig. 8.8 Thick epithelial lining with visible hair follicles and fibrofatty core

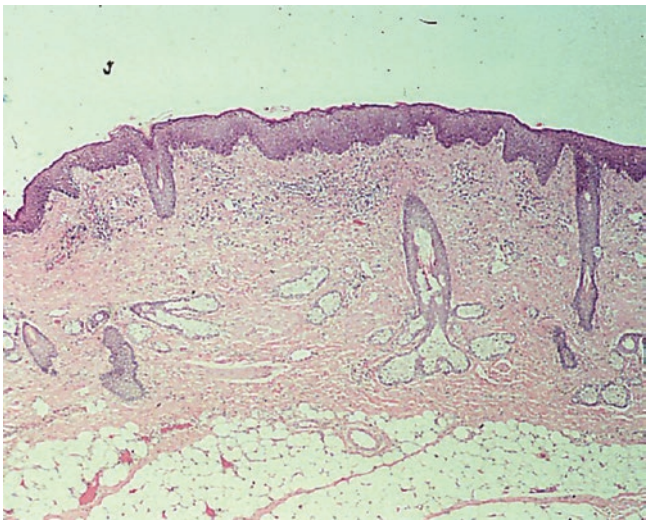

Fig. 8.9 The thick surface lining is keratinizing squamous epithelium with hair follicles

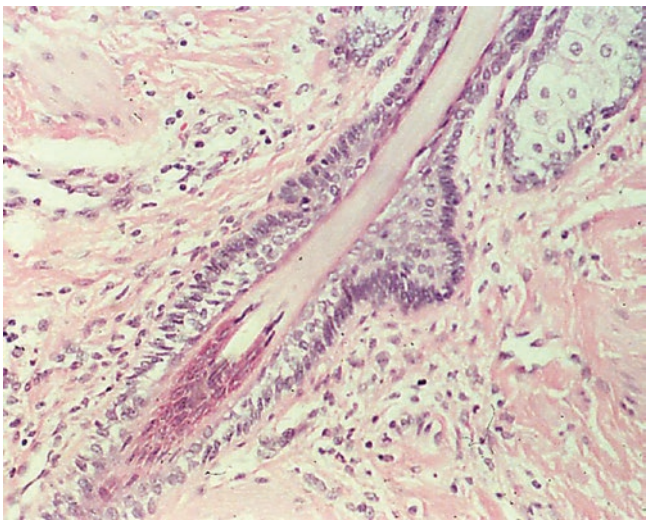

Fig. 8.10 Higher magnification of hair follicle and hair shaft

is classified as a benign lesion, although they are locally aggressive due to their capability of destructing and remodeling the surrounding bony structures [35, 36].

There are different theories to explain the growth and development of JNA. The most agreed on theory is that JNA develops from the chondrocartilage while the cranial bones are developing. It originates from the sphenopalatine foramen at the junction of the root of the pterygoid process and the horizontal ala of the vomer [37].

Due to the tumors gender selectivity and age of onset, research had initially focused on steroid hormones that included trials of estrogen treatment. These studies had variable results and response outcomes. Furthermore, flutamide was used, as well, as an antiandrogen treatment for JNA, but that did not show any major reduction in size preoperatively. Recently, specific receptors have been targeted for JNA treatment; this suggested that JNA might be depending on androgen. Others, bFGF, and transforming growth factor-beta-1, which were found in the stroma of the JNA, have also been used. Additionally, vascular endothelial growth factor (VEGF) and VEGFR-2 have also been found in JNAs [38–40].

Another focus of research was the tumor suppressor gene and its association with familial adenomatous polyposis coli (APC), which is located in chromosome 5q21. This gene regulates the level of b-catenin that has been implicated in producing some of the JNA stromal components. Additionally, b-catenin is a coactivator of androgen receptors that possibly increase the tumor's sensitivity to androgen [41].

As mentioned above, the tumor starts next at the sphenopalatine foramen. Large JNAs can be bilobed or dumbbell-shaped, with one side filling the nasopharynx and the other in the pterygopalatine fossa. There are various growth patterns for JNA thereafter. The anterior growth would bow the posterior wall of the maxillary sinus and invades into the anterior ethmoid cells superiorly. Further anterior growth can result into midfacial pressure and remodeling. Medial growth would fill the nasopharynx and nasal cavity, which can result into displacing the nasal septum to the contralateral side. Lateral growth goes into the pterygopalatine fossa and infratemporal fossa. Thereafter, it can extend to the inferior orbital fissure and greater wing of the sphenoid [42–44].

Superior growth of the JNA can involve skull base and pterygoid plates, as well as the body of the sphenoid. Intracranial extension can occur in about one third of the patients of the developed countries and more than two thirds of the developing countries [42–44]. There are five routes for intracranial extension or invasion of the JNA. These routes are:

- Direct extension through foramen rotundum, lacerum, and ovale.
- Infratemporal fossa to the middle cranial fossa.
- Pterygopalatine fossa through the inferior and superior orbital fissure to the middle cranial fossa.
- Cribriform plate to the anterior cranial fossa.
- Through the roof of the sphenoid sinus into the sella and to the cavernous sinus.

The blood supply of JNA comes from both external and internal carotid arteries. The former would feed the JNA through the internal maxillary artery, ascending pharyngeal artery and palatine arteries, and the latter would supply through the sphenoidal branches and ophthalmic artery.

Clinical Presentation

The most frequent symptom of JNA is nasal obstruction. This symptom is present in almost all cases. Epistaxis, especially when present in an adolescent boy, should make alarm the physician to investigate for a JNA. The epistaxis is usually unilateral and severe in nature. Up to 60% of the JNAs would present with epistaxis. When the nasal cavity and paranasal sinuses are blocked, the patient could have headaches, anosmia, rhinorrhea, and hyposmia. Hearing loss may be caused by Eustachian tube obstruction from the JNA occupying the nasopharynx. If the JNA is large, it could cause facial swelling and cheek deformity, and if it extends medially, it could cause palatal swelling and possibly trismus.

The orbit is occasionally involved either through the lamina papyracea or through the orbital fissure. When that occurs, proptosis and diplopia may be present.

Differential Diagnosis

The differential diagnosis of JNA depends on the presenting symptom; though this chapter is discussing the nasopharyngeal diseases, a focus on nasal and nasopharyngeal masses is warranted:

1. Nasal polyps.
2. Antrochoanal polyp.
3. Encephalocele.
4. Hairy polyp.
5. Rhabdomyosarcoma.
6. Nasopharyngeal carcinoma.
7. Esthesioneuroblastoma.

Radiological Features

Plain X-rays no longer needed or play a role in the diagnosis and work up of patients suspected to have JNA. CT scan is very important in highlighting the bony changes. Classically, JNA would appear as a lobulated mass centered on the sphenopalatine foramen. It could also show a nasopharyngeal mass, opacification of the sphenoid sinus, widening of the pterygopalatine fossa, erosion of the medial pterygoid plates, and anterior bowing of the posterior wall of the maxillary

sinus. The latter is a pathognomonic sign of JNA (Holman-Miller Sign). There is a marked enhancement following contrast injection. The usual appearance of the bone is of remodeling rather than destruction. This feature is helpful in differentiating between it and more aggressive cancerous lesions [45].

On MRI T1 weighted sequences, the mass would have an intermediate signal and adding gadolinium would give strong enhancement. T2 sequences show a heterogeneous signal intensity and flow voids. The presence of flow voids result in a salt and pepper appearance in the majority of the sequences. In addition, MRI is a great tool in the evaluation of the tumor extensions intracranially and into the orbit [45].

Angiography and angioembolization should performed preoperatively to help reduce the bleeding during surgery [45].

Management

Many staging systems have been described for JNAs. The most widely used system is that of Radkowski. There are other variations of this staging system, examples of these are the modified Fisch and the Snyderman for endoscopic resection of JNA.

There are several treatment options for JNA, but the treatment of choice remains complete surgical excision. Hormonal therapy with flutamide was reported to control the disease in up to 44% of the patients with some reduction in size. The use of flutamide did not get wide acceptance and utilization likely due to the controversial outcomes of patients in the literature. Furthermore, many of these patients present with an advance disease, which requires an urgent treatment.

There are several approaches for surgical resection. In the past, endoscopic approaches were used only for small and early tumors. This led to utilization of open approaches routinely. Nowadays, in the era of advancement in endoscopic instruments and intraoperative navigation systems coupled with the added experience in endoscopic sinus and skull base surgeries, many of these tumors are excised endonasally and endoscopically. Occasionally, endoscopic-assisted procedures are performed. In our institution, for example, when necessary a lateral buccogingival sulcus incision is made to help push the tumor from the infratemporal fossa back to the pterygopalatine fossa and into the nasal cavity while the second surgery is applying gentle retraction while dissecting endoscopically [46–48].

Open surgical approaches can be classified into anterior and lateral approaches (e.g., Fisch type D with facial nerve mobilization, preauricular infratemporal fossa approach). The anterior approaches can be subclassified into intraoral (e.g., degloving—Le Foor-1 with palatal translocation, degloving transpalatal, and degloving trans-antral) and facial incision approaches (weber-ferguson with facial translocation). The choice of the JNA location and extent in addition to the preference and experience of the surgical team [47].

Although radiotherapy is effective at controlling the disease, complications arising from it limited its utilization. These complications include secondary malignancies and panhypopituitarism, as well as the challenge in operating in a radiated field [49].

Excluding hemorrhage and ophthalmic complications, most of the postoperative complication is specific to the technique used or the extent of the disease. Rarely, malignant transformation can occur and has been reported in six cases in the literature [50].

After treatment, children with JNA are followed closely. Symptoms and thorough physical examination including nasal endoscopy are often unreliable. For that reason, serial imaging (CT and MRI with contrast) is necessary in the surveillance. MRI with gadolinium is very sensitive in detecting disease residual and recurrence.

Case Presentation

A 13-year-old male presented with nasal obstruction, headache, and recurrent epistaxis. A nasal endoscopic examination demonstrated a fleshy mass obstructing the left nasal cavity posteriorly. A CT scan revealed a vascular lesion in the posterior nasal cavity, nasopharynx, and pterygopalatine fossa. The posterior wall of the left maxillary sinus was bowed anteriorly (Fig. 8.11). Angiography and embolization were performed preoperatively and the lesion was excised through a transfacial approach (Figs. 8.12 and 8.13).

The histopathology is below (Figs. 8.14, 8.15, 8.16 and 8.17).

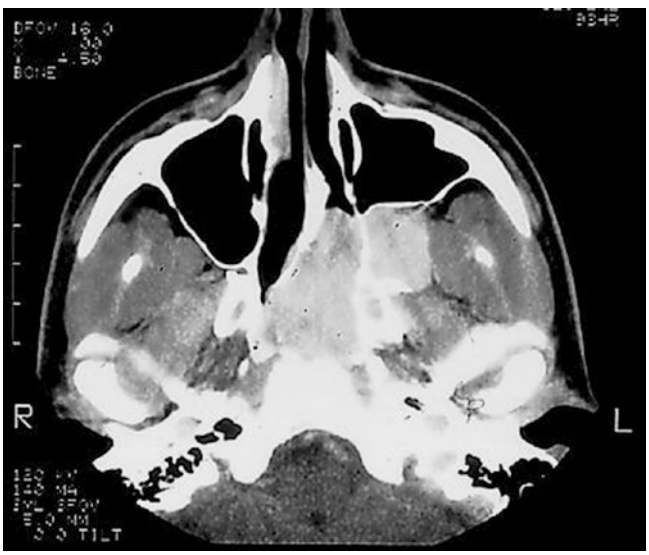

Fig. 8.11 Axial CT showing enhancing mass in posterior nasal cavity, nasopharynx, and pterygopalatine fossa. The posterior wall of the left maxillary sinus is bowed anteriorly

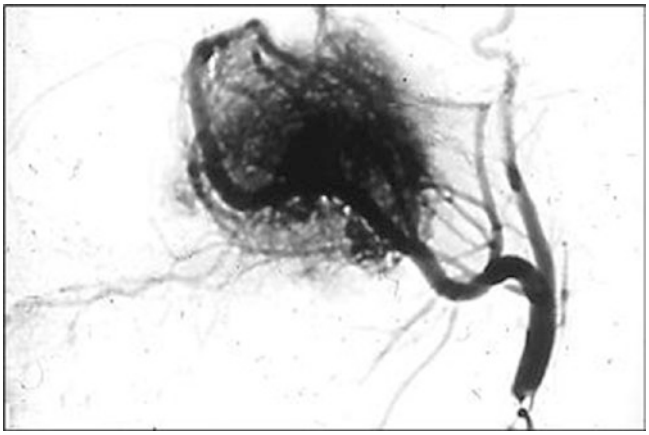

Fig. 8.12 Carotid angiogram showing vascular supply from external circulation

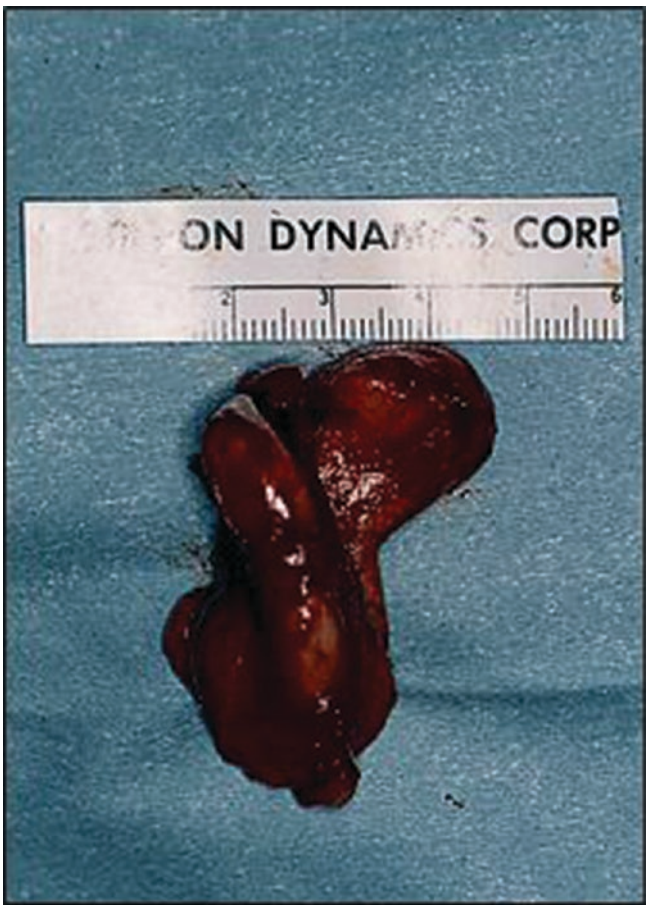

Fig. 8.13 Gross appearance of lesion

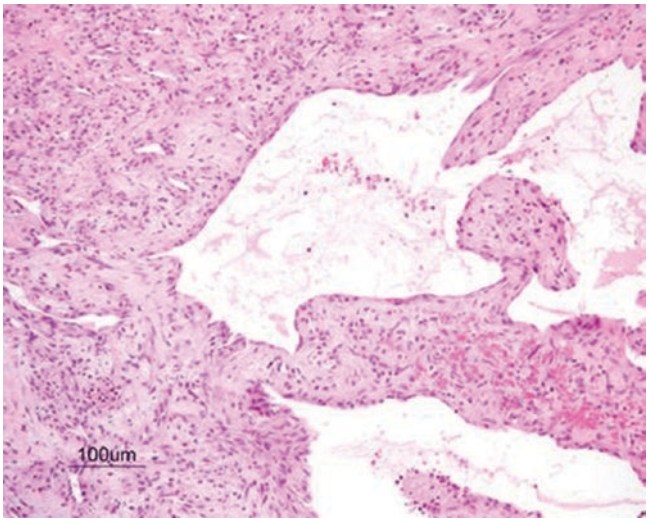

Fig. 8.14 Cavernous area within angiofibroma

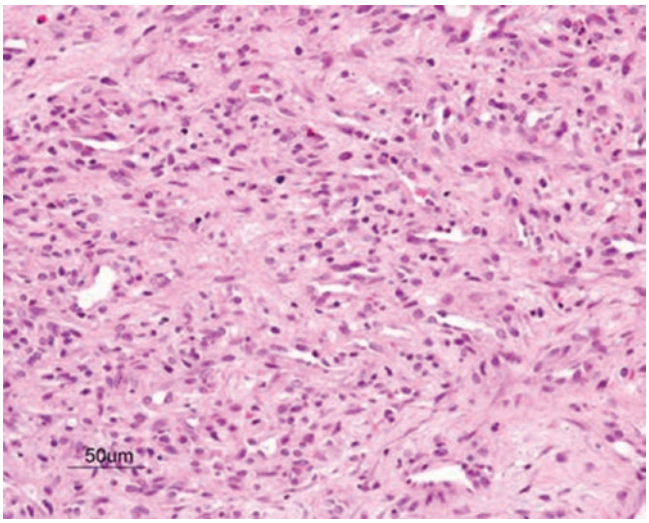

Fig. 8.15 Compact cellular area within angiofibroma

Pituitary Tumors

Definition (Classification/Subtypes, Epidemiology, Genetics, Etc.)

Pituitary diseases were first described in the late 1800s by Pierre Mari (Paris, France). He reported on two patients with findings of acromegaly. Pituitary tumors are common diseases in adults, though less so in children, recognizing their clinical presentations is essential as they carry favorable outcome if identified and managed appropriately. They constitute up to 15% of all intracranial tumors. Pituitary adenomas are responsible for 90% of all pituitary tumors [51].

Various oncogene abnormalities are thought to be involved in the pituitary diseases and tumorigenesis. Abnormalities and mutations in G-Protein, *p53* gene deletions, and *ras* gene mutations, in addition to the association of pituitary tumors and multiple endocrine neoplasia syndrome (MEN syndrome), of which have been involved in the development of pituitary adenomas [52].

Most of the pituitary tumors are benign in nature, but in certain occasions and depending on the genesis of the tumor,

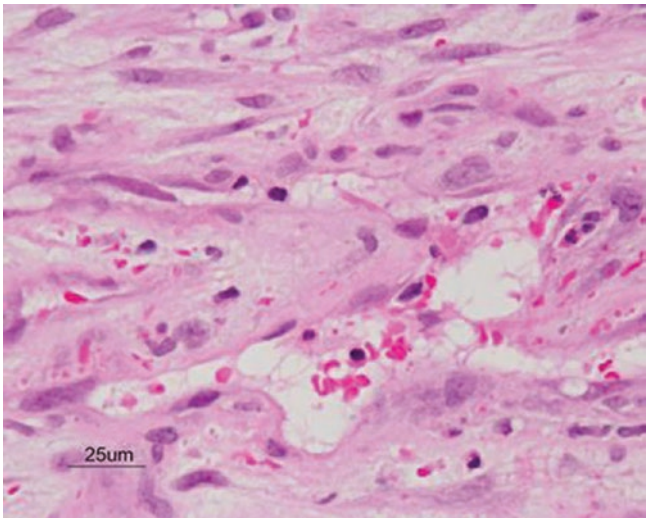

Fig. 8.16 Higher magnification of stroma of angiofibroma. This figure shows the vascular spaces have a simple lining. The stroma is loose and edematous and contains bland appearing spindle cells (upper part of the figure)

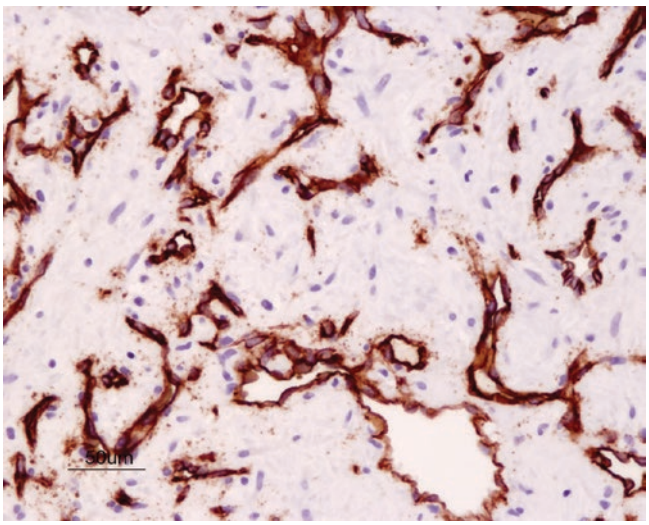

Fig. 8.17 Immunostain for endothelial cell marker CD34 shows the ectatic vascular spaces are lined by a single layer of endothelial cells

these neoplasms may grow in a rapid manner and be more aggressive. For an example, *p53* gene deletion is associated with aggressive tumors. The clinical presentations of children with pituitary tumors are either due to mass effect of the tumor on the surrounding structures or the distant features of endocrine abnormalities affecting various organs. Most of the pituitary adenomas are not controlled by hypothalamic releasing factors and hormones [52].

Pituitary tumors can be classified into microadenomas (<1 cm) and macroadenomas (>1 cm). Another classification is nonfunctioning and functioning tumors based on the hormone secretions. Examples of functioning (or hormone secreting tumors) include prolactinoma, gigantism, acromegaly (mostly in adults), and Cushing's disease.

A less used classification is based on the histological staining where the tumor is classified into chromophobic and chromophilic [53–55].

Clinical Presentation

Children with pituitary adenomas would present with either symptoms pertaining to endocrinological imbalance or mass effect from the tumor. Patients with prolactinoma have hypogonadism, amenorrhea, galactorrhea and infertility in women; and decreased libido, impotence, and galactorrhea in men. Patients with Cushing's disease have centripetal obesity, weight gain, violet striae, moon facies, easy bruising, myopathy (proximal), and psychiatric symptoms. Additionally, they may also have hypertension, diabetes, cataract, osteoporosis, and glaucoma. Similarly, deficiency of hormones can be a presenting feature, though usually patients would present later. Rarely, pituitary apoplexy may happen, and it is often catastrophic [55].

Optic chiasm compression and changes in vision is one of the main mass effect features of pituitary macroadenomas. The optic chiasm is anatomically located above the pituitary gland in most children. A macroadenoma growing superiorly will abut the chiasm and compress it. This compression will result in the classic bitemporal hemianopia. The main complaint the patient would present with is accidentally bumping into objects or frequent car accidents [55].

Another feature of macroadenomas include cavernous sinus invasion. In some instances, macroadenomas feature invasive growth or extension into the cavernous sinus. Most of these tumors are prolactinomas. If cavernous sinus invasion is present, complete resection becomes less feasible. Compression on other cranial nerves (oculomotor and abducens) can also happen.

Differential Diagnosis

The differential diagnosis of pituitary tumors is a list of space occupying tumors in that region. The most common diagnoses to be considered are:

1. Craniopharyngioma.
2. Saccular cerebral aneurysm.
3. Pituitary metastasis.
4. Pituitary carcinoma.
5. Meningioma.
6. Rathke's cleft cyst.

Radiological Features

Pituitary adenomas can be either diagnoses due to clinical presentation, or incidentally, on imaging, while investigating another disease. On CT scan, a mass variable density is shown depending on the nature of the adenoma (cystic/solid); it also demonstrates moderate enhancement with contrast, rarely calcifications may occur. MRI is the best imaging modality to assess the pituitary tumor. It is capable of

delineating the mass and clearly visualizes the optic chiasm and surrounding structures. Both T1 and T2 weighted images; the adenoma is isointense to the gray matter. If large, it can be heterogeneous due to the cystic component or necrosis and hemorrhage. It also demonstrates moderate to strong enhancement with gadolinium. T2 with gradient echo is sensitive for determining any hemorrhagic components of the mass [12].

On PET scan, normal pituitary does not show any increased uptake, but macroadenomas are highly hypermetabolic on both choline and FDG tracers.

Management

In tumors that are functioning, medical care is started to fix the hormonal imbalance. The majority of prolactinomas respond to dopamine receptors agonist. This results in improvement in the visual field, reduction, and sometimes resolution of symptoms associated with hyperprolactinemia in addition to reduction of the size of the adenoma. Somatostatin analogues are useful in acromegaly, especially during the postoperative period [56].

Central compartment skull base surgery has gone through an evolution since the days of Harvey Cushing. Nowadays, endoscopic transnasal approach is able to adequately and safely address most pituitary adenomas.

The surgical technique includes either by approaching the sphenoid sinus through the natural ostium or by performing an ethmoidectomy. Often the latter is used if wider exposure is needed. After a wide sphenoidectomy and posterior septectomy, the sella is then opened and the tumor is resected. If CSF leak is encountered, a repair is performed using a combination of fat, fascia lata, muscle, and septal flap.

These children require close follow-up by the endocrinologist both in the pre- and postoperative periods to manage the hormonal imbalance.

Occasionally, stereotactic radiosurgery is used. The main complication of using it is hypopituitarism. Less faced complications include damage to the optic nerve, other cranial nerves, and the carotid artery.

Although these patients generally have a very good outcome, recurrence is common. Up to 18% of patients with pituitary adenoma will have recurrences requiring an intervention [56].

Craniopharyngioma

Definition (Classification/Subtypes, Epidemiology, Genetics, Etc.)

Craniopharyngiomas are dysontogenic lesions that have benign histological features but malignant behaviors. They invade surrounding structure and recur after complete resection. The most frequent location of origin is the pituitary stalk, specifically from Rathke's pouch, and they often project into the hypothalamus [57]. Craniopharyngiomas extend laterally along the path of least resistance; anteriorly to the prechiasmatic cistern, posteriorly to cerebellopontine angle, and laterally to the subtemporal spaces [57].

There are various theories behind the etiology of craniopharyngiomas. The embryologenetic theory focuses on the development of the adenohypophysis and the transformation of Rathke's pouch remnant. The metaplastic theory relates to the remnant of the squamous epithelium, which may undergo metaplasia. The dual theory discusses that the spectrum of craniopharyngioma are caused by either one of the previous theories. The childhood onset of craniopharyngioma to be caused by the embryologenetic theory, and the adult onset is caused by the metaplastic theory.

The overall incidence of craniopharyngioma is <0.5 per 100,000 persons. It also accounts for 4% of all childhood tumors. There are two pathological variants of craniopharyngiomas: adamantinomatous and papillary [57].

Clinical Presentation

Craniopharyngiomas are typically slow growing tumors with variable presentation depending on its location and size. The usual presentation is similar to that of a pituitary adenoma, which includes visual disturbance, hormonal imbalance, and headache. If extension to the nasopharynx is present, children may present with rhinological symptoms including nasal obstruction, rhinorrhea, and purulent discharge. These symptoms are often confused with those of adenoid hypertrophy [57].

Differential Diagnosis

1. Pituitary adenoma.
2. Rathke's cleft cyst.
3. Intracranial teratoma.

Radiological Features

On CT scan, these tumors appear cystic with solid component and usually calcification. Craniopharyngioma enhances strongly with contrast. On MRI, T1 sequence shows a hyperintense tumor that has vivid enhancement with gadolinium. T2 weighted images have variable intensity [58].

Management

The treatment of craniopharyngioma is usually surgical resection with and without radiotherapy. The Surgical approach is similar to that of a pituitary adenoma, but occasionally a craniotomy is needed. In some patients who are not surgical candidates, gamma knife can be used as a primary modality of treatment [57].

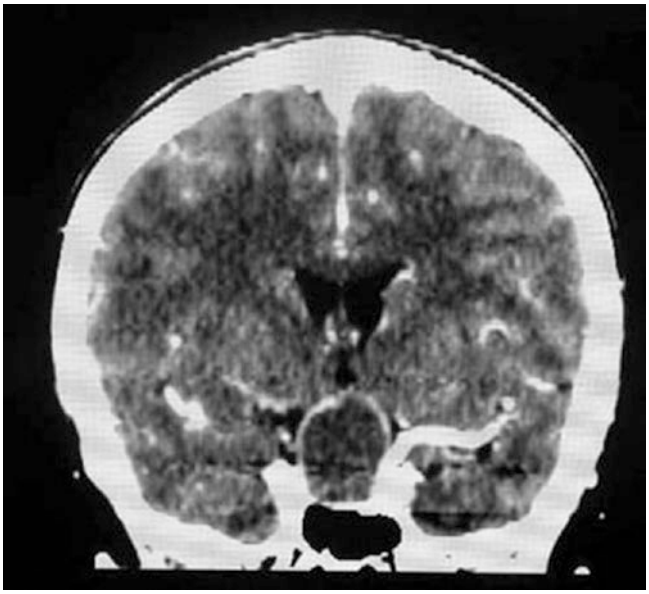

Fig. 8.18 Coronal CT showing lesion in the sellar region

One third of the patients may recur with adamantinomatous craniopharyngioma having a higher recurrence rate compared to the papillary variant.

Case Presentation
A 12-year-old male presents with a 2-year history of headache and intermittent nausea and vomiting. Endocrinological workup revealed hypothyroidism and hypocortisolism. Imaging revealed a cystic lesion in the sellar region. A transsphenoidal biopsy and drainage was performed with the neurosurgical service. Intraoperative findings included an encapsulated mass with a solid and fluid component consisting of yellow-green fluid and crystals (Figs. 8.18, 8.19, 8.20, 8.21, 8.22 and 8.23).

Malignant Tumors

Non-Hodgkin Lymphoma

Definition (Classification/Subtypes, Epidemiology, Genetics, Etc.)

Lymphoma is defined as leukemic cells tumor extending beyond the site of the bone marrow while not involving more than 25% of the bone marrow itself. Lymphoma is the third most common malignancy of childhood. More than 60% of all childhood lymphomas are non-Hodgkin's lymphoma (NHL) [59, 60]. The incidence of NHL in the first decade of life is 7 per one million childbirths. There is a 3:1 male predominance and twice as common in Caucasians compared to African descendants. In comparison to adult lymphomas, Lymphoma of childhood is primarily extranodal disease.

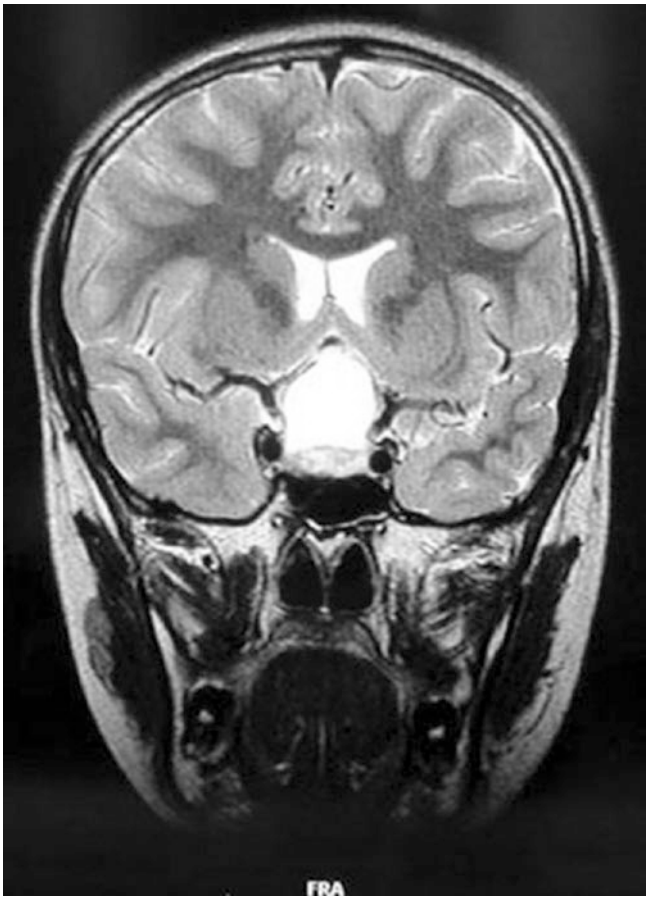

Fig. 8.19 Coronal T2 showing cystic nature of the mass, bright on imaging

NHL is subdivided into different types depending on immunophenotype, molecular biology, and response to treatment. The three most common subtypes to present in childhood are mature B-cell NHL (also known as, Burkitt lymphoma or diffuse large B-cell lymphoma), lymphoblastic lymphoma, and anaplastic large cell lymphoma. The remainder of the subtypes of NHL tends to be rare in the pediatric population. Molecular biological markers have helped differentiate the subtypes and help aid the diagnosis. For example, one of the classic markers in NHL is the translocation of the *myc* gene from chromosome 8 to 14 and less commonly to chromosomes 2 or 22. This is typically found in Burkitt's lymphoma. Another molecular marker is the rearrangement of t(2;5) chromosome that is found in most large-cell lymphomas [61–64].

The literature is scarce when it comes to discussing risk factors of developing childhood NHL, though some factors and populations have been found to be at a higher risk. Compromised immunity, whether due to congenital or acquired disease, increases the risk of NHL. Some of these conditions include Wiskott–Aldrich syndrome, ataxia-telangiectasia, X-linked lymphoproliferative disorder, and

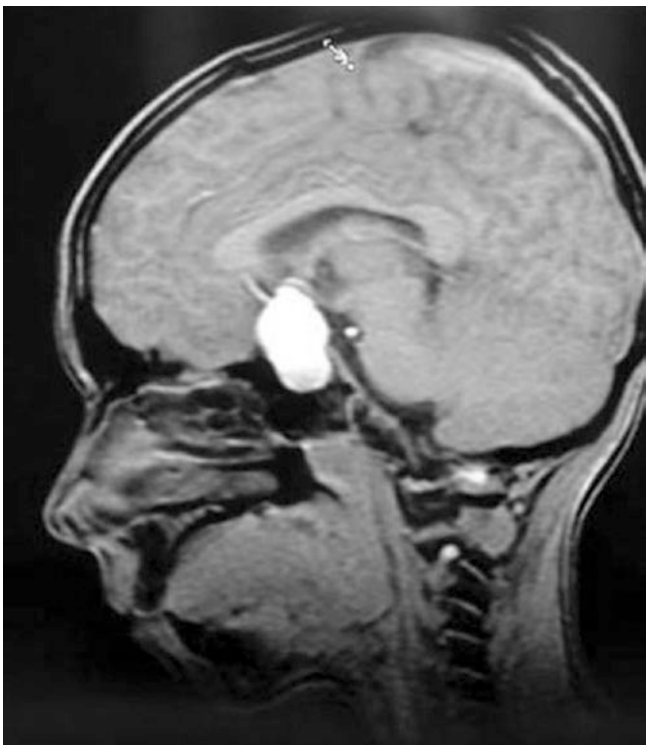

Fig. 8.20 Sagittal T2 MRI showing bright signal suggesting cyst in suprasellar region

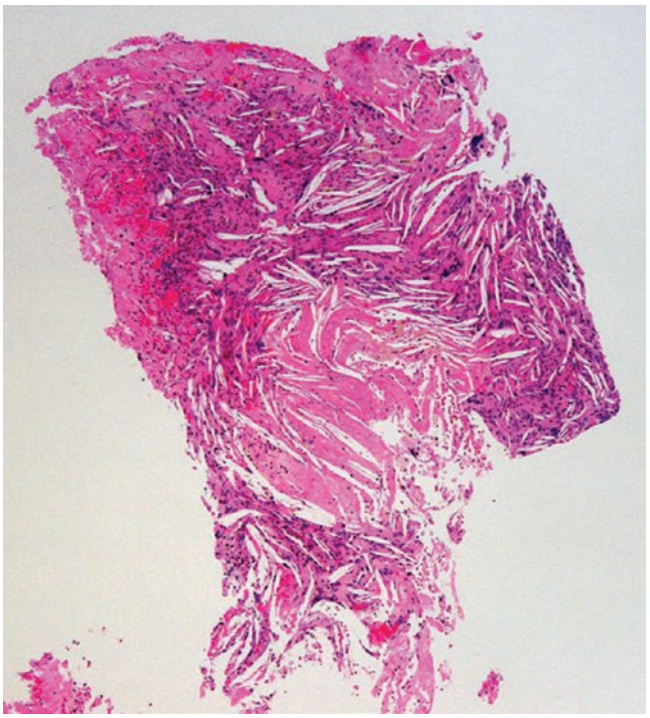

Fig. 8.21 Low magnification shows a cholesterol granuloma in this adamantinomatous craniopharygioma. Unfortunately, the lining epithelium is degenerated

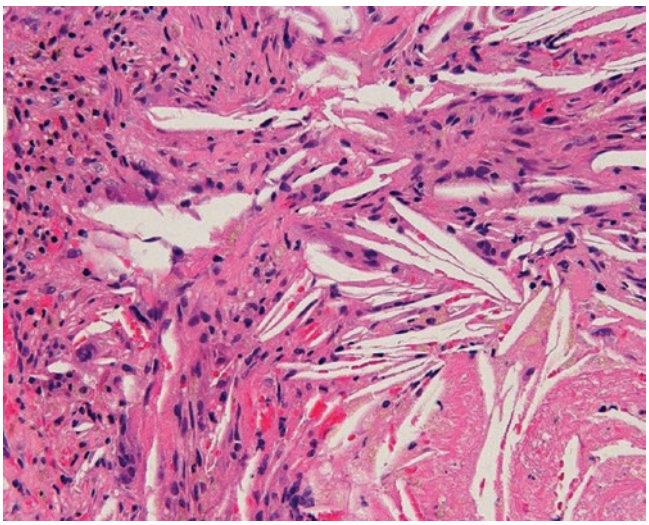

Fig. 8.22 Condensed needle-shaped structures represent cholesterol crystalline deposits that caused a chronic granulomatous inflammation

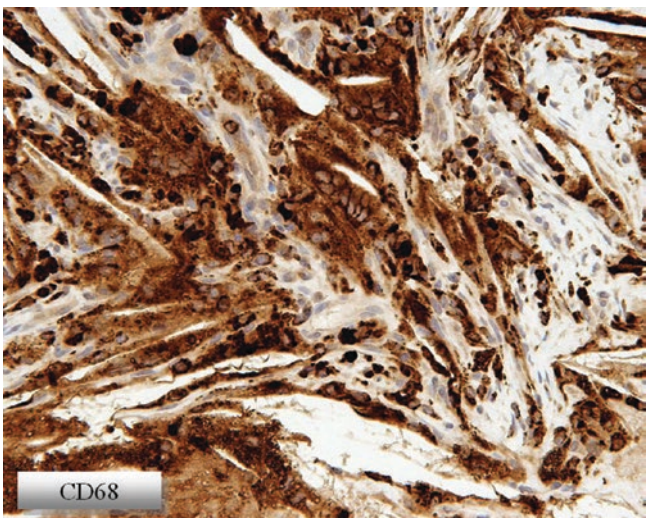

Fig. 8.23 The chronic granulomatous inflammation contains CD68-positive giant histiocytes shown by immunostain

acquired immunodeficiency syndrome (AIDS) [65]. The most common sites of developing NHL in children are the mediastinum, abdomen, and head and neck. The nasopharynx is the second most common location in the head and neck for NHL presentation. Epstein–Barr virus (EBV) is associated with many of the NHL cases diagnosed in immunocompromised patients. The majority of Burkitt lymphoma in Africa is EBV associated; this incidence is much more than Burkitt lymphoma diagnosed in the United States and Europe.

Clinical Presentation

NHL of childhood can have either an acute or subacute presentation; this is in contrast to NHL in adults with the presentation is more of indolent course. For that reason, children with NHL usually average less than 6 weeks from the time of presentation to diagnosis [66]. The bone marrow involvement can result in bone pain, fatigue, and cytopenia. Nasopharyngeal NHL would present with symptoms of space occupying lesion. Nasal obstruction, snoring, rhinorrhea, and purulent discharge may be present. Additionally, night sweats, low-grade fever, malaise, anorexia, and decrease appetite are other common symptoms in nasopharyngeal lymphoma. When the CNS is involved, the child may have headache, cranial nerve palsies, sensory deficits, and meningeal signs.

On physical exam, nasopharyngoscopy would show an adenoid-like tissue occupying the whole nasopharynx. The tonsils and lingual tonsils may be enlarged. Cervical lymphadenopathy can be present, as well.

If disseminated disease, other sites can be involved as well. For an example, a mediastinal mass and abdominal mass may result in dyspnea and abdominal pain, respectively. One of the presentations of Burkitt's lymphoma is tumor lysis syndrome. This condition is a result of a rapid breakdown of malignant cells, which causes various metabolic abnormalities, including hyperuricemia, hyperkalemia, and hyperphosphatemia. Tumor lysis syndrome can either be the presenting symptom or more commonly it can present after the diagnosis but prior to the start of the treatment [66].

Differential Diagnosis

Conditions to be considered in the differential diagnosis of nasopharyngeal NHL are those of similar symptoms and anatomical locations.

1. Tuberculosis.
2. Atypical mycobacterium infections.
3. Rhabdomyosarcoma.
4. Lymphoproliferative disorders.
5. Infectious mononucleosis.

Radiological Features

Whenever lymphoma is suspected in the differential diagnosis of a nasopharyngeal mass, general radiological work is needed to both assess the nasopharyngeal mass, as well as evaluate other regions involvement in the disease.

A chest X-ray is the basic examination to rule out hilar lymphadenopathy and pulmonary parenchymal lesions. CT scan of the head and neck would show a nasopharyngeal mass that is consistent with enlarged adenoid tissue. The suspicious finding of lymphoma on CT is the asymmetry in the location, though typically either centrally located or bilaterally involving. Other more specific finding suggestive of lymphoma is involvement of other regions, namely, the cervical lymph nodes and mediastinum. Another benefit of CT scan is to assess for intracranial involvement of the lesion; further assessment of the intracranial involvement, if present, may require an MRI. Ultrasound of the abdomen is needed to rule out or assess abdominal masses [67–69]. PET scan is highly recommended in patients with NHL. Most NHL is 2-[fluorine-18]fluoro-2-deoxy-d-glucose (FDG) avid; this enables assessment of the response to treatment using this modality. This has been a new trend in most of the new lymphoma chemotherapy protocols [70].

Furthermore, an echocardiography is usually performed as a baseline assessment prior to receiving chemotherapy that may include anthracyclines, which may cause cardiomyopathy.

Management

In the work up of a patient with suspected NHL of the nasopharynx, serological testing of CMV and EBV are performed. Lactate dehydrogenase levels (LDH) are requested as well, although recent studies have shown that patients with head and neck lymphoma have lower levels of LDH compared to non-head-and-neck disease. For that reason, an elevated LDH could indicate a disseminated disease. The mainstay for diagnosis of nasopharyngeal NHL is a nasopharyngeal biopsy or a cervical lymph node excisional biopsy. Bone marrow assessment is performed by an aspiration and biopsy, with bilateral bone marrow biopsy being superior to unilateral biopsy. As previously mentioned, if the bone marrow biopsy indicates more than 25% involvement of the bone marrow, it is diagnostic of acute leukemia.

The most accepted staging system for NHL is St. Jude Children's Research Hospital Classification that is based on the Ann Arbor Staging system [71].

Stage 1: Single extranodal tumor or single anatomic location (nodal)—Mediastinum and abdomen are excluded.
Stage 2: Single extranodal tumor with regional node involvement; primary gastrointestinal tumor; 2 or more nodal regions on the same side of the diaphragm, or 2 single extranodal tumors with or without regional nodes on the same side of the diaphragm.
Stage 3: Mediastinal, pleural, or thymic primary tumors; extensive and unresectable abdominal tumor; paraspinous or epidural tumors, 2 or more nodal regions on both sides of the diaphragm, or 2 single extranodal tumors with or without regional nodes on both sides of the diaphragm.
Stage 4: CNS or bone marrow involvement.

The treatment for an aggressive NHL, for example, diffuse large B-cell lymphoma has evolved throughout the years. Nowadays, the treatment includes chemotherapy with immunotherapy in addition to targeted radiotherapy. The

current guidelines from the national comprehensive cancer network (NCCN) is to either provide three cycles of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) with an anti-CD 2 monoclonal antibody rituximab (R-CHOP) in addition to involved area radiotherapy, or six to either cycles of R-CHOP with or without radiotherapy [72]. For advanced stage NHL, R-CHOP, rather than CHOP, is considered the standard of care in many centers in North America. However, the cure rate with R-CHOP ranges from 30% to 70%.

When tumor lysis syndrome is present, hydration and allopurinol or rasburicase are necessary components of treatment in all patients. Caution should be taken when treating patients with G6PD deficiency as rasburicase can cause methemoglobinuria and hemolysis [66]. Hyperuricemia with tubular obstruction may cause acute renal failure that could require dialysis. This is not considered a contraindication to continuing the chemotherapy. In general, surgery is not indicated as a treatment modality in NHL unless airway is compromised that would require an urgent or planned tracheostomy to secure the airway.

One of the challenging in treating NHL of childhood is managing relapses. Recently, induction regimens that include new chemotherapy combinations such as ifosfamide, etoposide, and carboplatin are being used. Occasionally, myeloablative chemotherapy with autologous stem-cell rescue or bone marrow transplantation may be required.

Rhabdomyosarcoma

Definition (Classification/Subtypes, Epidemiology, Genetics, Etc.)

The most common soft tissue sarcoma in the pediatric population is rhabdomyosarcoma (RMS) [73]. It represents 13% of all childhood malignancies. Furthermore, it is the third most common pediatric neoplasm. The annual incidence of RMS in pediatric is 4.5 cases per one million children, one third of which present in the head and neck. The sites that are mostly involved are orbit, nose, paranasal sinuses, nasopharynx, soft tissue, external ear, and mastoid. Due to the proximity and higher risk of central nervous system (CNS) involvement, the paranasal sinuses, infratemporal fossa, middle ear, and nasopharynx are referred to as parameningeal [73].

There are three main histological subtypes and the incidences of the disease vary to them. These subtypes are as follows:

- Embryonal: This is the most common subtype of RMS. Embryonal RMS are predominantly males (F: M = 1:2) most of which happen by the age of 4 years.
- Alveolar: This subtype incidence does not vary due to age. The overall incidence is ~1 case per million children.
- Undifferentiated Sarcoma: Infants younger than 1 year have the highest incidence of developing undifferentiated sarcoma. Most of which are in the trunk and abdomen.

Usually, RMS occurs sporadically, though patients with embryonal tumors are often associated with high birth weight in addition to large size to gestation age. There are some genetic conditions associated with RMS. The most common one is Li-Fraumeni cancer susceptibility syndrome. This syndrome has DICER1 mutation [74]. Others include neurofibromatosis type 1, Costello syndrome, Wilms' tumor, hepatoblastoma, and Beckwith-Wiedemann syndrome.

Clinical Presentation

RMS presentation varies depending on the location. Nasopharyngeal RMS symptoms are mainly those of nasopharyngeal obstruction, including nasal obstruction, rhinorrhea, purulent nasal discharge, epistaxis, middle ear effusion, in addition to cranial nerve palsy. Anemia, pain, and fatigue alongside enlarged neck lymph nodes are also features of the disease. Nasopharyngoscopy will show a mass occupying the nasopharynx. Often the mass is submucosal. A rapidly developing proptosis could indicate orbital involvement.

Differential Diagnosis

The differential diagnosis of RMS of the nasopharynx is focused on malignant looking space occupying lesions.

1. Lymphoma.
2. Chordoma.
3. Nasopharyngeal Carcinoma.
4. Adenoid Cystic Carcinoma.

Radiological Features

The appearance of RMS is nonspecific and often indistinguishable from other sarcomas. On CT scan, RMS would appear as a soft tissue density that has some enhancement with contrast. CT scan is useful in searching for metastasis especially in the chest. In over 20% of the cases, adjacent bony destruction is seen. On MRI, T1 sequence would show a low to intermediate intensity to the adjacent muscles. It is not uncommon to see areas of hemorrhage in the alveolar subtype. RMS enhances strongly with gadolinium. On T2 sequence, RMS is hyperintense with prominent flow voids. ^{99m}Tc bone scan is performed and bone marrow aspirate are used to rule out metastasis.

Management

After confirming the diagnosis and staging the tumor, multimodality–multiagent therapy is the management's mainstay

for RMS. Many different agents are used in the chemotherapy regimen. The dose and the type are dictated by the location of the tumor and the extent of the disease. For example, local orbital RMS would require 2 or 3 agents that are less intensive. Whereas patients with metastatic disease would benefit from high intensity 3 agents treatment regimen. Radiation therapy is needed to eradicate the residual primary tumor. The typical dose for nasopharyngeal RMS is 4500–5500 cGy. Hyperfractionation did not prove to have better long-term control compared to standard fractionation. Surgery is reserved for biopsy and for surgically accessible disease. With the advancement in skull base techniques, the surgical resection of primary tumors has gained more popularity. This has the benefit of reducing the late side effects of radiation.

The survival of RMS varies depending on the site, histological subtype, and stage. Overall, the 5-year prognosis and survival is around 75% [75].

Case Presentation

A 4-year-old female presented with a 2-week history of nasal congestion, blood-tinged rhinorrhea, and worsening obstructive sleep apnea. Intra-oral examination revealed a large nasopharyngeal mass extending into the oropharynx as shown in the CT image. An urgent biopsy was performed that confirmed a diagnosis of embryonal rhabdomyosarcoma, Botryoid-type (Figs. 8.24, 8.25, 8.26, 8.27, 8.28 and 8.29).

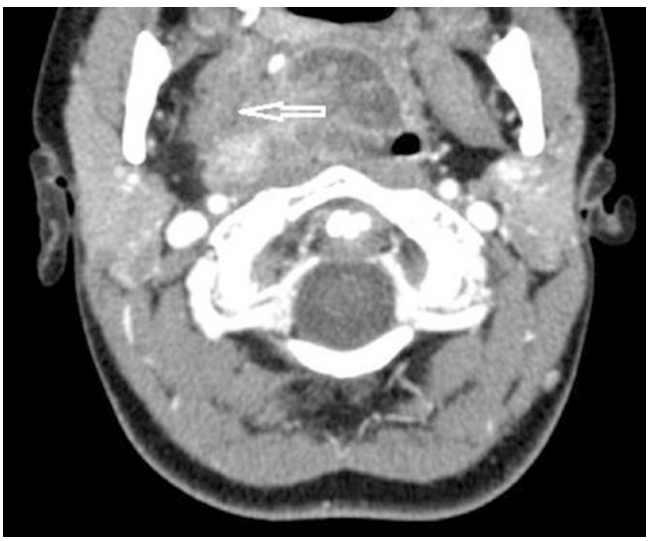

Fig. 8.24 Contrast-enhanced axial CT shows large obstructive mildly enhancing heterogeneous mass in oronasopharynx. Note loss of fat space definition of pterygoid muscle on the right side (arrow)

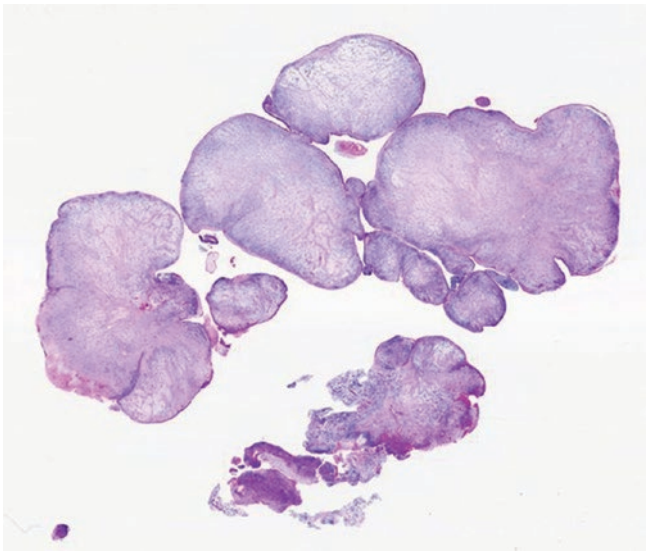

Fig. 8.25 Fleshy polypoid cellular growths replaced the normal mucosa

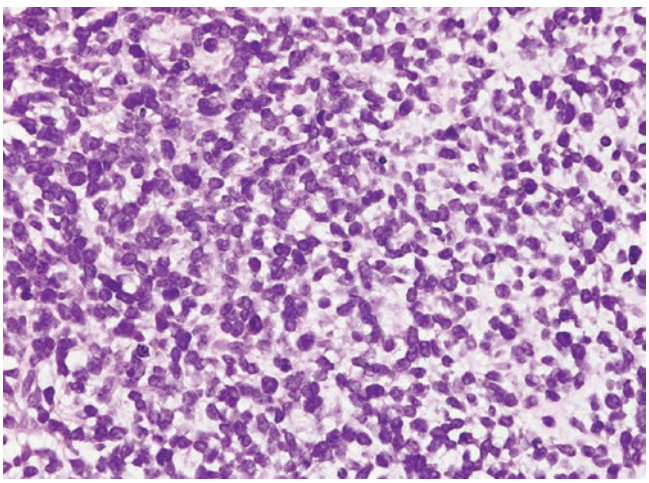

Fig. 8.26 Typical appearance of small, round, blue cell tumor infiltrates seen at high magnification

Chordoma

Definition (Classification/Subtypes, Epidemiology, Genetics, Etc.)

Chordomas are rare malignant tumors that account for 4% of all primary bone tumors. Chordomas develop from the embryonic remnant of the primitive notochord. Since they originate from bone, they are usually extradural and cause local bone destruction. Although they are aggressive locally, they rarely metastasize. The three most common sites are sacrococcygeal, spheno-occipital (clival), and vertebral bodies [76, 77].

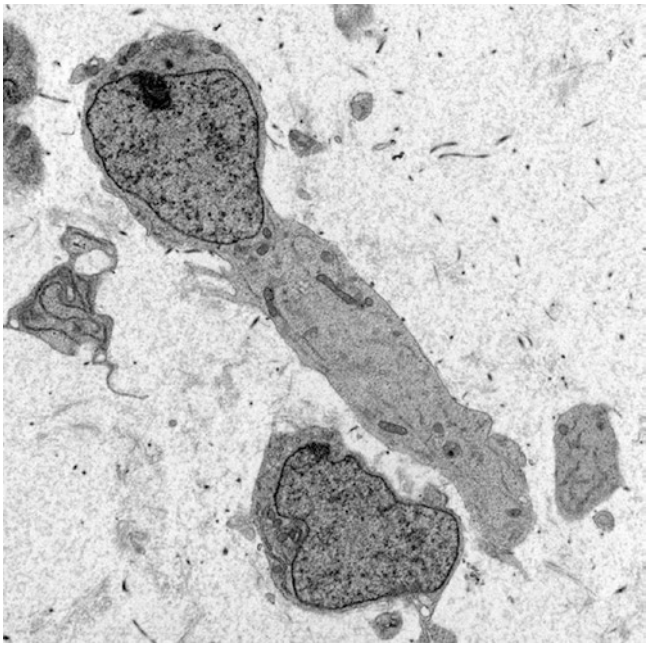

Fig. 8.27 Electron micrograph of a primitive tumor cell with a tail of cytoplasm trailing a small spherical nucleus. Such feature resembles that of a strap cell of rhabdomyosarcoma. Typically, in this primitive stage of differentiation, only a few intermediate filaments are seen in the cytoplasmic tail. No thick and thin filamentous bundle with Z-bands that are characteristic of contractile filaments of a differentiated skeletal muscle fiber is present

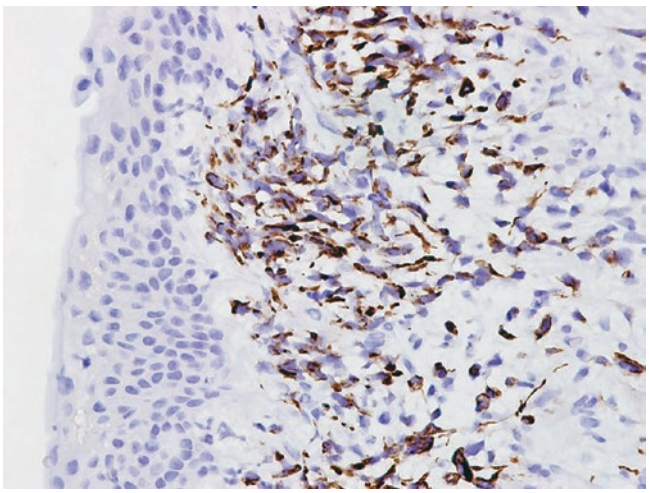

Fig. 8.28 Immunostain for desmin, an intermediate filament present in skeletal muscle or myofibroblasts are demonstrated in the cytoplasm of the tumor cells

They occur at any age, but they are rare seen in children. They are commonly found in Caucasians [76].

Clinical Presentation

Similarly to RMS, chordomas present with symptoms pertaining to the mass effect on the surrounding structures. Clival chordoma would present with nasal obstruction, purulent nasal discharge, headaches, and cranial nerve palsies, including hoarseness and diplopia. The diagnosis is suspected with nasopharyngeal endoscopy and only confirmed with histological assessment of a biopsy.

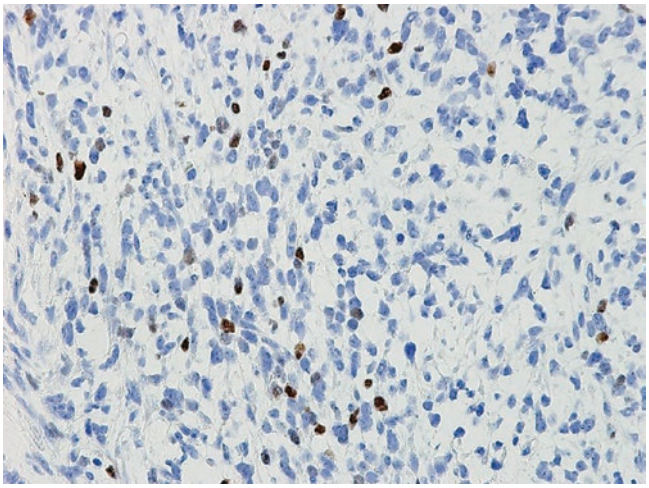

Fig. 8.29 Immunostain for myogenin. A subset of tumor cells demonstrate activation of transcription factor myogenin that initiates muscle cell differentiation. This low-density staining of tumor cells is a characteristic feature of embryonal rhabdomyosarcoma. In the other subtype of rhabdomyosarcoma (alveolar rhabdomyosarcoma), a much higher density of myogenin positively stained nuclei are seen

Differential Diagnosis

Clival chordoma differential diagnosis involves solid lesions occupying the nasopharynx and skull base.

1. Chondrosarcoma of the skull base.
2. Plasmacytoma.
3. Meningioma.
4. Pituitary macroadenoma.
5. Nasopharyngeal carcinoma.

Radiological Features

Patients with suspected chordoma should get both MRI and CT scan, as they are complementary to each other in the tumor evaluation. The CT scan evaluates the degree of bone destruction and involvement and the calcification pattern inside the lesion. The chordoma would appear centrally located, well circumscribed, and feature destructive lytic lesion with some marginal sclerosis. Additionally, it could also present as an expansile soft tissue mass. This mass would be hyperattenuating relative to the brain. It would also be heterogeneous due to cystic necrosis and hemorrhage. Intramural calcification that appears irregular can be present. Chordomas in general enhances well.

MRI would demonstrate three-dimensional view of the posterior fossa, sella turcica, and cavernous sinus. On T1-weighted sequences, chordoma has intermediate to

low signal intensity, mucous pool or intratumoral hemorrhage would appear as small foci of hyperintensity. T1 with gadolinium demonstrate a heterogeneous enhancement with a honeycomb appearance. This appearance corresponds to the low T1 signal foci inside the tumor. T2 weighted sequences would exhibit high-intensity signals. Gradient echo views would confirm the presence of hemorrhage with blooming. Bone scan is often ordered, and chordomas would have either normal or decreased uptake [78, 79].

Management

Chordoma is treated by surgical resection. The operation involves teamwork between an otolaryngologist and a neurosurgeon. The surgical approach is either an anterior midline subfrontal approach or an endoscopic nasal approach. Temporary, and sometimes permanent, cranial nerve palsy is a risk of this surgery due to the delicate dissection around the brainstem and the vertebrobasilar system. Residual tumor, if present, should receive proton beam radiotherapy [80]. Tumor recurrence is common, especially around the operative tract. For that reason, some centers advocate the use of radiotherapy even in the presence of complete surgical resection. The prognosis of chordoma is not high. The approximate 10-year survival is 40% [78].

Case Presentation

A 10-year-old female presented with dysphagia and a progressively enlarging retropharyngeal mass. A transoral biopsy was performed demonstrating a chordoma. Definitive excision required a midline mandibulectomy and tongue split (Figs. 8.30, 8.31, 8.32, 8.33, 8.34 and 8.35).

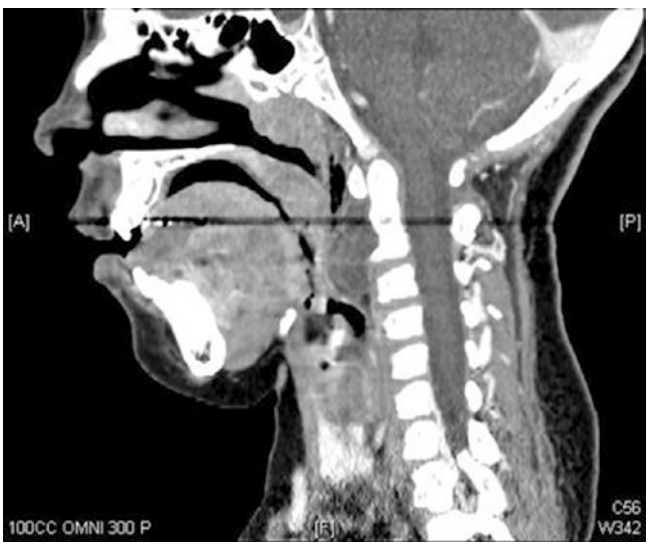

Fig. 8.30 Sagittal CT shows multiseptated mass in prevertebral space

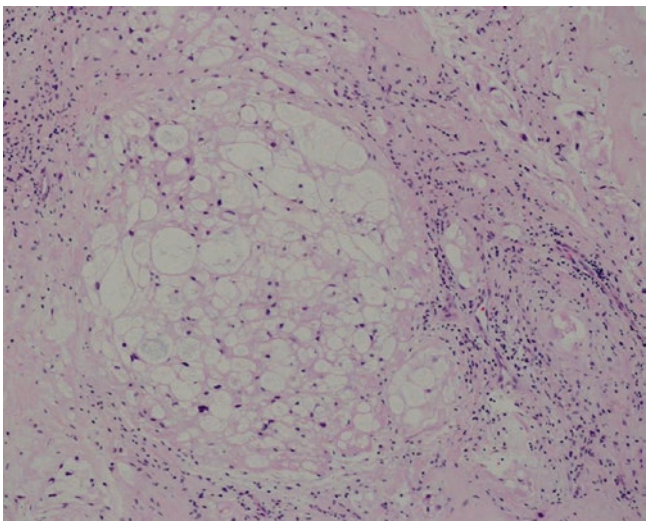

Fig. 8.31 Cross-section of a cord of cells, which has voluminous amounts of vacuolated cytoplasm. These cells have been given a designated term as "physaliferous"

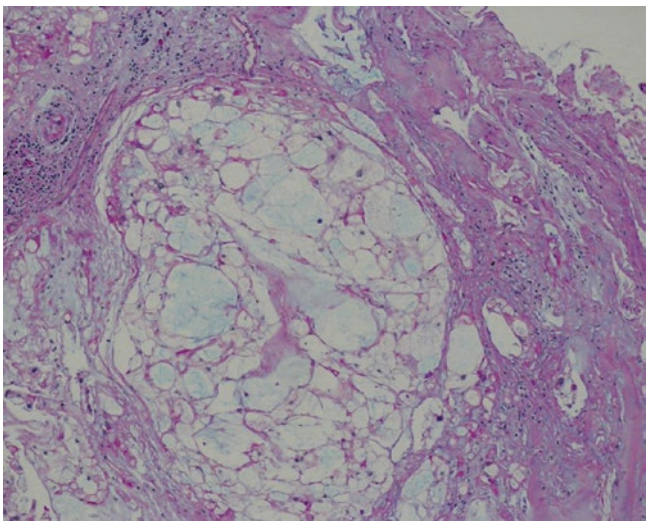

Fig. 8.32 As shown here, the cytoplasm of physaliferous cells contains mucin contents (stained blue) that is demonstrable by mucin PAS stain

Nasopharyngeal Carcinoma

Definition (Classification/Subtypes, Epidemiology, Genetics, Etc.)

Nasopharyngeal carcinoma (NPC) is an uncommon pediatric malignancy. It accounts for 1% of all pediatric malignancies. The incidence in the pediatric population is less than 1:100,000. It occurs more frequently in ethnic Chinese in the southern of China and Inuits of Alaska. Other regions with higher than average incident include Malay, India, North Africa, and the Middle East. NPC has a higher prevalence in males with ratio of approximately 2:1.

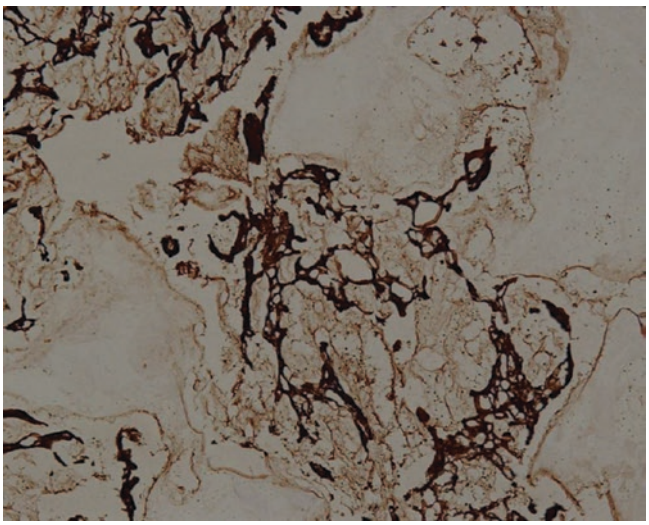

Fig. 8.33 Cytokeratin. Chordomas are positive for cytokeratin by immunostain

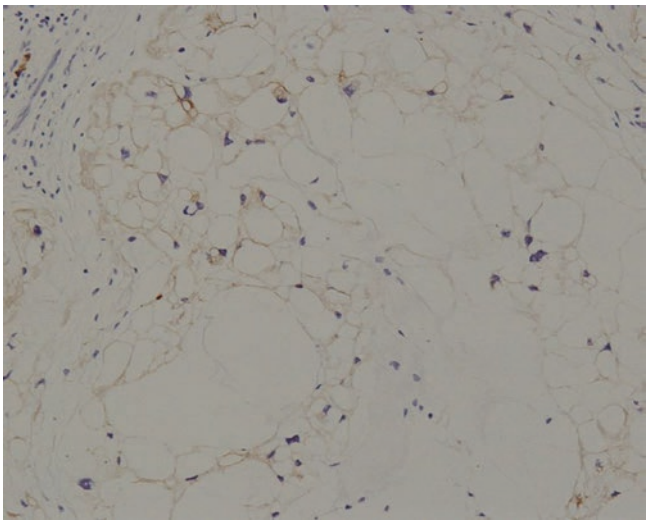

Fig. 8.34 Nuclear staining of chordoma cells (brown superimposed on the blue color nuclear staining pattern) seen with S100 immunostain. Not shown is the same staining pattern with Brachury immunostain

There are three main etiologies associated with NPC. These are environmental, genetic factors and Epstein–Barr virus (EBV). It is not well understood if there is one specific factor that induce the development of NPC, but the current hypothesis is that it is a combination of the above 3 etiologies [82].

Evidence points toward a strong association with genetic predisposition. First-degree family members have almost eight times the risk of developing NPC compared to the general population. In 1975, an association of HLA alleles and NPC was established. This was noted on HLA A, B, & D on chromosome 6. Furthermore, HLA A2, B 17, Bw46, Bw58, DRe, and DR9 have been found more in patients with NPC

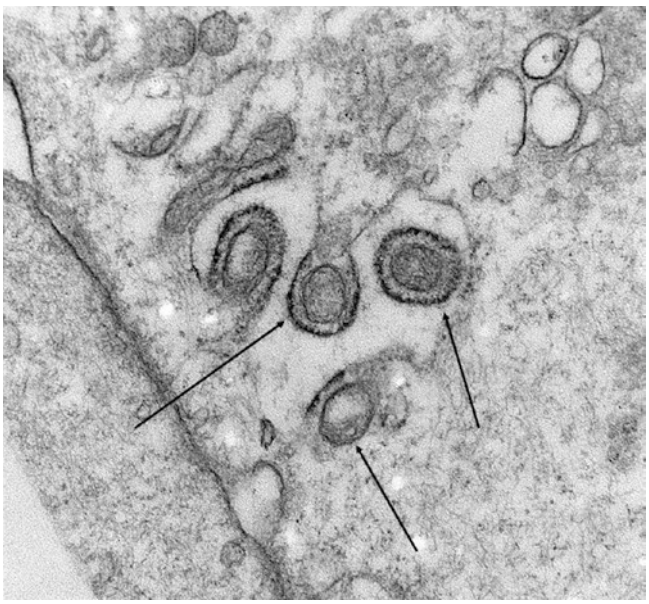

Fig. 8.35 Electron micrograph showing the presence of mitochondria surrounded by endoplasmic reticulum (the so called mitochondrial rough endoplasmic reticulum complexes [81])

consistently more than the general population. Additionally, many Chinese with NPC do not have HLA-A0201 rather they have HLA-A0207 haplotype [83, 84].

Some of the chromosome changes described include chromosome 3, 9, and 11 deletions, though the significance of these deletions and chromosomal anomalies is yet to be well understood. Other chromosomal anomalies have been detected that pertains to tumor suppressor genes, that gave rise to research focusing in developing targeting therapy for NPC.

Diet is the most common environmental factor associated with NPC. It is thought that diet high in preservatives is associated with NPC. This includes salted vegetables and fish. In large series epidemiological studies, it is believe that early exposure, especially during weaning, carries the highest risk of developing NPC. Other factors include wood dust and chemical fumes. Thus far, no relationship has been identified between smoking and developing NPC [85].

EBV has been found on NPC cells. Although the majority of the population in the world has been infected with EBV, in NPC the viral capsid antigen (VCA) and the early antigen (Ea) are raised. It also expresses both lytic and nuclear antigens, these includes Epstein–Barr nuclear antigen (EBNA-1 to 6). It is believed that EBNA-1 is the responsible for maintaining episomes of the virus in the tumor cells. Furthermore, NPC expressed Epstein–Barr encoded ribonucleic acids (EBERs). Normal nasopharynx does not express these EBV antigens. For these reasons, the theory is that EBV does not initiate NPC, rather an element in a multifactorial environment that results in triggering the development of NPC [86, 87].

The world health organization has published an NPC classification 1978. This classification got updated twice. The latest publication in 2005 classifies them as [88]:

- Type 1: Keratinizing squamous cell carcinoma.
- Type 2: Non-Keratinizing Carcinoma.
  - Type 2a: Differentiated type.
  - Type 2b: Undifferentiated type.
- Type 3: Basaloid squamous cell carcinoma.

Clinical Presentation

NPC is usually diagnosed when the patient is symptomatic. Incidental diagnosis of NPC accounts for about 1%. This is usually noted during imaging for other cases; 75% of the patients are male. Approximately 15% of the patients will present with a first-degree family history of NPC.

The commonest presentation of NPC is with a neck mass. This is true for all age groups of NPC. These lumps are due to disease metastasizing to the neck lymph nodes prior to diagnosis. These pathological lymph nodes are often matted in nature. Level 5 and 2b neck nodes are likely where the lump will likely be present. Nevertheless, the sentinel node for NPC is usually the retropharyngeal node. Other less common lesions are level 2 and level 3, whereas level 1a is extremely rare. Occasionally patients may present with intraparotid lymph node metastasis [89–93].

Epistaxis and blood-stained saliva are the second most common presenting symptoms after neck lump. This is due to the tumor bleeding either anteriorly (epistaxis) or postnasally (blood stained saliva). Almost as common is hearing loss due to otitis media with effusion. Older children, and more often adults, presenting with unilateral middle ear effusion should be screened for NPC for obstructing the Eustachian tube. Therefore, hearing loss is conductive in nature in these patients who may also complain of tinnitus. Clival extension may result in headaches, and cranial nerve palsy likely represents and advance disease. The most common cranial nerves to be involved are the sixth, fifth, 12th, ninth, and 10th. If at presentation the patient presented with diplopia, this may be caused by edema of the surrounding tissue and not necessarily invasion. This diplopia is often reversible after treatment with radiotherapy.

On rhinoscopy, NPC is identified as an exophytic mass occupying the nasopharynx. In some occasions, when the mass is small, it is feasible to identify that the lesion is originating from the fossa of rosenmuller. The mass may be ulcerating and/or bleeding [89–93].

Differential Diagnosis

When incidentally found on imaging, the differential diagnosis involves any mass or tumor involving the nasopharynx.

If the tumor is small, the differential diagnosis include:

1. Adenoid hypertrophy.
2. Lymphoma.
3. Early nasopharyngeal malignancy.

If the tumor is large with skull base involvement:

1. Adenoid cystic carcinoma.
2. Plasmacytoma.
3. Lymphoma.
4. Chordoma.
5. Fibrosing pseudotumor.
6. Chondrosarcoma.
7. Meningioma.
8. Pituitary macroadenoma.

Radiological Features

Although NPC is diagnosed using a biopsy, imaging is essential in staging the disease by highlighting the extent and the spread of the disease (nodal and distant metastases). As mentioned earlier, fossa of rosenmuller is the initially effaced and that most of the patients would present with lymph nodes involvement, likely in the retropharynx, level II and level V.

The advantage if using CT scan in investigating NPC is that it is readily available and that it aids detecting bone involvement. Though if the tumor is small and confined in the nasopharynx, CT scan might not able to differentiate between NPC and adenoid hypertrophy. Larger tumors are easier to diagnose as they show mass effect and invasions to the surrounding structures including skull base, Eustachian tube, foramen lacerum, and ovale in addition to direct extension through the clivus, cavernous sinus, and temporal bone. With contrast, the primary tumor and the metastatic involved lymph nodes tend to enhance heterogeneously. Although retropharyngeal lymph nodes tend to be the first region to be involved, in 35% of the cases, the retropharyngeal lymph nodes are skipped and level II or V gets involved first. After treatment with radiotherapy, postoperative radiotherapy changes and fibrosis can mimic tumor residual on CT scan.

To further demonstrate soft tissue details, an MRI is needed. With MRI, perineural spread may be detected in addition to bone marrow infiltrations. Similarly, dural changes and involvement can be detected as well. On T1 and T2 sequences, NPC is typically isointense, but on T2 fat saturation is helpful. T1 with gadolinium shows fat saturation and heterogeneous update of the tumor itself in addition to perineural extension if present. Contrarily to CT scan, MRI is capable of differentiating post radiotherapy fibrosis from residual tumor. Fibrosis, if mature, would appear hypointense on T2 and does not demonstrate any enhancement with gadolinium, though early fibrosis can be mistaken for residual as it can be hyperintense on T2 and may demonstrate gadolinium enhancement. Positron emission tomography

(PET scan) is the best modality to detect recurrence, and it is also highly sensitive for detecting nodal metastasis [94, 95].

Management

As any other tumor, the gold standard of diagnosis is acquiring a biopsy sample for histological assessment and confirmation. The biopsy is usually taken using a rhinoscopy under local anesthesia. In some occasions, nodal fine needle aspiration cytology would confirm the cancerous process, but the nasopharyngeal biopsy is negative. In these occasions, the patient is taken to the operating room, and under general anesthesia, the nasopharynx is then reexamined and a deep nasopharyngeal biopsy is undertaken.

After confirming the diagnosis, the patient is staged using the imaging modalities mentioned above. An audiogram and tympanogram is useful in patients with NPC to document pretreatment hearing and also to detect middle ear effusion that would require treatment with pressure equalizing tubes. EBV serology is performed including IgA VCA and IgA Ea. Pretreatment dental assessment is also performed.

Stage 1 disease is typically treated with radiotherapy alone. Stages 2–4 are treated with both chemotherapy and radiotherapy, either with induction chemotherapy or concurrent treatment. When chemotherapy is used, a cisplatin-based chemotherapy has shown clear survival benefit and is considered the gold standard chemotherapy drug for NPC.

Surgery is usually reserved for recurrence cases, which occurs in ~10% of all newly diagnosed patients with NPC. Local recurrence may be dealt with using re-radiation or by salvage surgery. Re-radiation, increase the risk of transverse myelitis, temporal bone necrosis, severe trismus, sensorineural hearing loss and choanal stenosis lower cranial nerve palsies. For that reason, re-radiation is reserved only for aggressive recurrence that is not amenable for surgical resection.

There are various approaches to address surgical resection. Recently with advancement in endoscopic surgical techniques, endoscopic surgical resection is usually utilized for small to medium size recurrences. Recurrence that extends beyond soft palate, pterygopalatine fossa is likely too extensive to be resected endoscopically. If considered amenable for endoscopic resection, it is important to resect the room of the nasopharynx and drill down the vomer and to the prevertebral muscles. Once the frozen section is adequate, the nasopharynx is packed for at least 1 week.

If the tumor is slightly larger and not amenable for endoscopic approach, a lateral rhinotomy and medial maxillectomy approach is utilized. If this approach does not provide adequate exposure, then a maxillary swing is used. The approach involves performing a Weber-Ferguson incision, and osteotomies are performed in a manner to allow the maxilla to rotate laterally without hindering its blood supply through the skin and subcutaneous tissue. Other approaches include lateral infratemporal and Le Fort 1. These are less common procedure and not often used for nasopharyngeal tumor resection.

When recurrence is regional, radical neck dissection should be performed. The risk of performing a neck dissection in these radiated patients is developing infections and bleeding. Furthermore, risk of carotid blowout is higher. For the reason, utilizing a pedicle-flap (e.g., pectoralis major flap) may prevent the development of wound dehiscence, and it acts as another protective layer over the great vessels [96–102].

Case Presentation

A 16-year-old male presented with bulky cervical adenopathy and a retropharyngeal mass that extended to the skull base. At presentation, he had several neurologic findings including a right Horner syndrome, 12th cranial nerve palsy, and paralyzed right vocal fold. He also had a right middle ear effusion. Imaging demonstrates the primary mass and the adenopathy. Pathology confirmed a diagnosis of undifferentiated, nonkeratinizing nasopharyngeal carcinoma that was associated with Epstein–Barr virus (Figs. 8.36, 8.37, 8.38, 8.39, 8.40, 8.41, 8.42, 8.43 and 8.44).

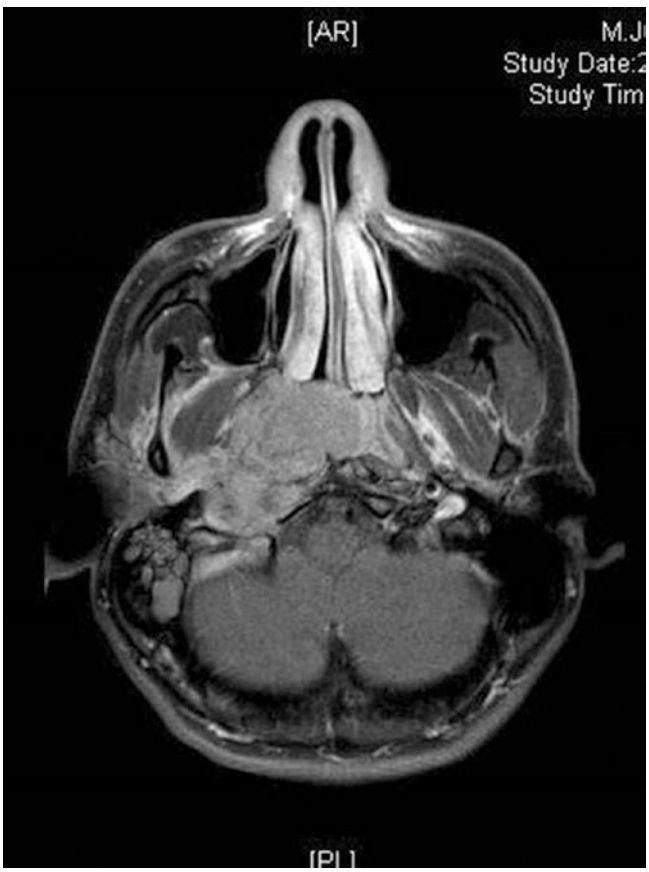

Fig. 8.36 Axial MRI T1 shows large mass in nasopharynx and destruction of the skull base. Note chronic mastoid changes likely secondary to Eustachian tube obstruction

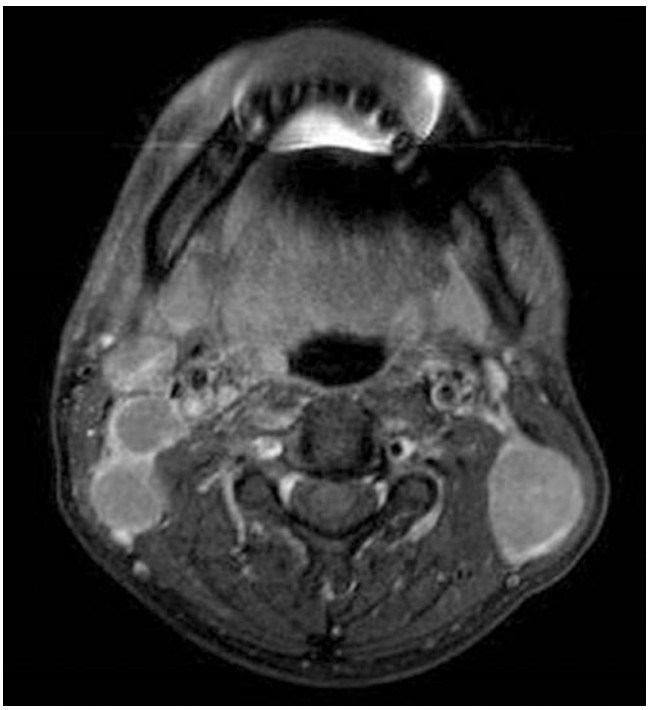

Fig. 8.37 Axial MRI T1 showing bilateral adenopathy representing metastatic disease

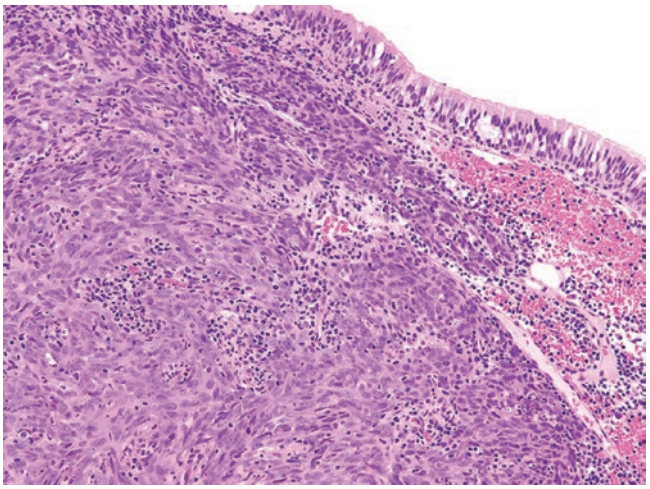

Fig. 8.38 A syncytial plumb spindle to polygonal epithelial cellular infiltrate is seen within the mucosa. It has an associated component of small lymphoid cells (seen as intermingling clusters)

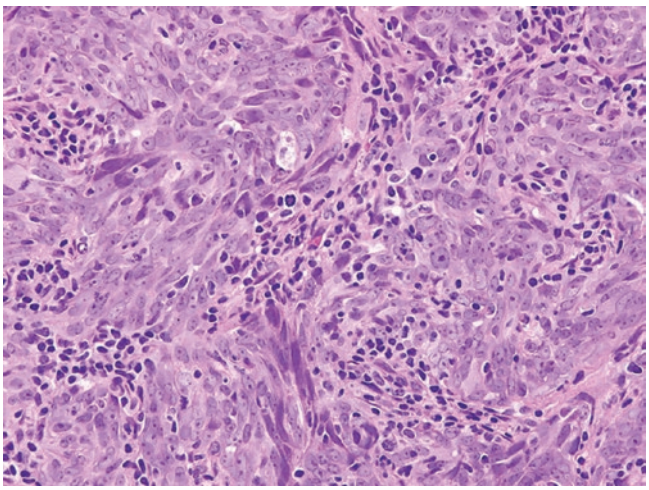

Fig. 8.39 Higher magnification of Fig. 8.38, same description

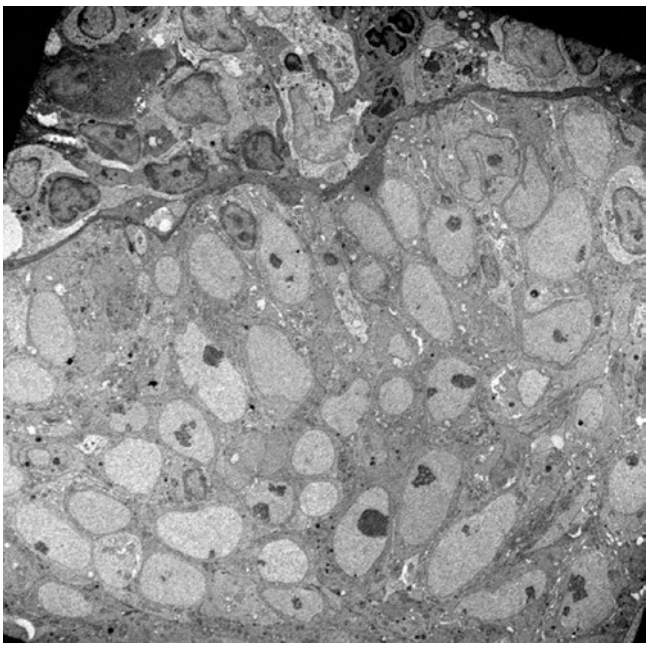

Fig. 8.40 Electron micrograph showing the cohesive cell nests have features resembling poorly differentiated squamous cells: oval nuclei with dispersed chromatin, occasional large nucleolus, absent keratohyalin granules in their cytoplasm. Some dilated rough endoplasmic reticulum is noted, and all cells form poor junctional complexes. Most of them lack the expected appearance of the normal desmosome

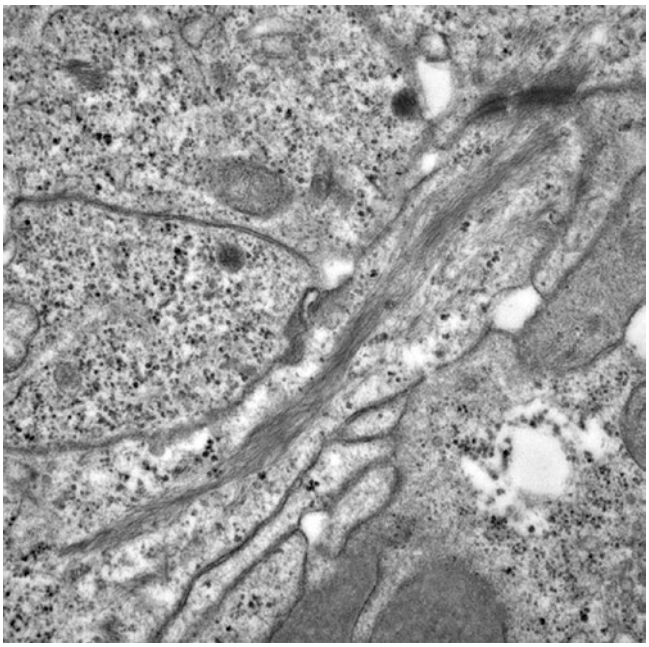

Fig. 8.41 High magnification electron micrograph. Shown are tumor cells (in the center) which fail to form a normal desmosome (in contrast to the two normal ones at the 1 o'clock region of the figure). The cytoplasm of one tumor cell lying in the diagonal plane of the figure contains a long intertwined cytokeratin filamentous bundle. Glycogen rosettes are present in the cytoplasm of the tumor cells

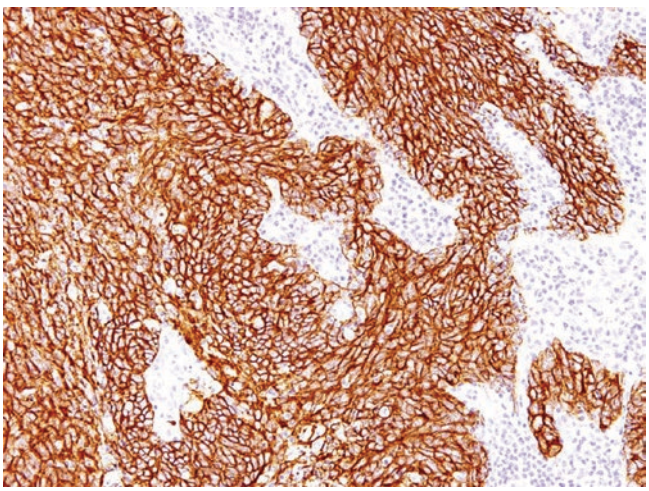

Fig. 8.42 Pancytokeratin. Positive cytokeratin immunostain supports the epithelial cell nature of the tumor cells

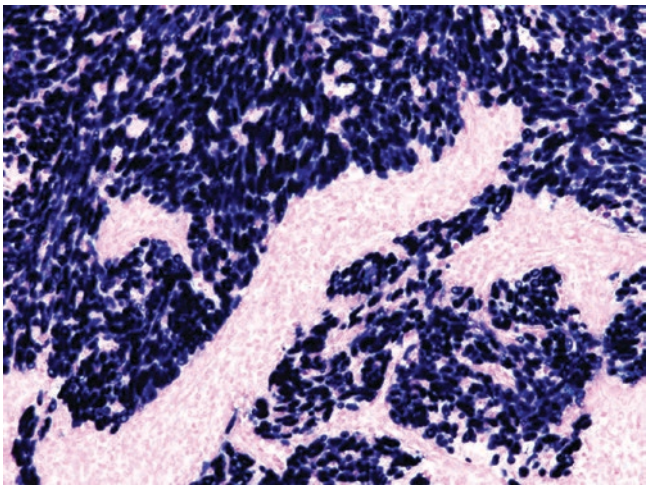

Fig. 8.43 EBER. All tumor cells contain Epstein–Barr virus associated RNA as demonstrated by in situ hybridization of EBV-encoded RNA (EBER stain)

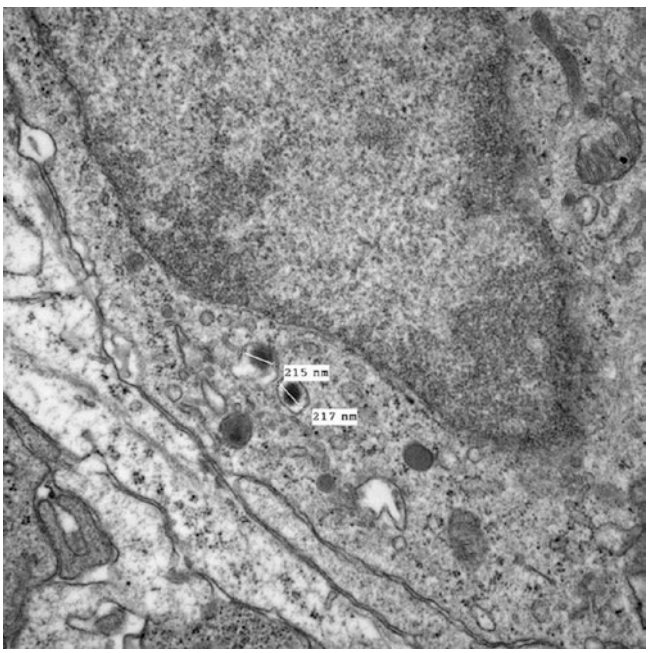

Fig. 8.44 High-magnification electron micrograph annotated with calibrated measurement of herpes virus type-size intracytoplasmic particles within a tumor cell

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