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Treatment of fibro-osseous lesions at the pediatric skull base ☆

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Fibro-osseous lesions of the pediatric skull base are loosely associated group of bony lesions that are all uncommonly occurring clinical entities. Management differs significantly amongst the fibro-osseous lesions but clinical and radiographic presentation can overlap significantly. Fibro-osseous lesions include fibrous dysplasia, ossifying fibroma, osteoma, and aneurysmal bone cyst in addition to even less common lesions such as giant cell tumor of bone and osteosarcoma. In this chapter, the fibro-osseous lesions affecting the pediatric skull base will be reviewed with an emphasis on the clinical, radiographic, and management differences between diagnoses.

Introduction

There is a loosely associated group of rare pathologies impacting the bony portions of the paranasal sinuses and skull base whereby normal osseous structures are replaced with fibrous tissues. This group, known as fibro-osseous lesions, is not unified in pathogenesis or management but associated insofar as they impact the bony anatomy similarly. In this chapter, fibro-osseous lesions impacting the pediatric cranial base are reviewed with an emphasis on appropriate diagnosis and management and the unique aspects of each pathology. Additionally, the unique characteristics of management of these lesions in the pediatric patient will be highlighted.

Clinical presentation

The presentation of fibro-osseous lesions varies widely and is both location and pathology dependent. Lesions can arise either directly within the bones of the cranial base or within the osseous structures of the orbit, paranasal si-

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nuses, or maxilla with superior extension to involve the cranial base. Symptoms at presentation may be absent as is the case when the lesion is identified incidentally on imaging for another indication but when present can range from nasal obstruction to subtle cosmetic deformity to cranial nerve deficit to proptosis. When symptomatic, visual symptoms such as diplopia and proptosis are most common, present in up to 80%[1] at the time of diagnosis. Vague complaints such as headache and sinonasal complaints including nasal obstruction and recurrent sinusitis are also commonly present, seen in 43% and 14%, respectively.[1] Painless swelling is another common presenting symptom, especially in fibrous dysplasia.[2,3] Over time, lesions may progress to the point of narrowing neural foramina, resulting in vision loss, oculomotor dysfunction, or alterations in sensation.[3] More aggressive lesions such as ossifying fibroma, aneurysmal bone cyst, and osteosarcoma have a greater propensity to present with cranial neuropathies earlier in their course.[4]

Clinical and radiographic evaluation

Clinical and radiographic evaluation of fibro-osseous lesions at the pediatric skull base should identify both the physical extent and the functional impact of the lesion. A history collected should be directed at understanding the timeframe for symptom development, evaluating cranial nerve function, and determining the presence of nasal obstruction or chronic sinus-related symptoms. In the first decade, the pediatric patient may not be able to elucidate these historical data efficiently, but most cranial nerve function data can be reliably obtained on exam. A history of significant injury at the site of lesion would raise concern for post-traumatic fibro-osseous reparative lesion.[5] History of prior radiotherapy or oncogenic syndromes such as Li-Fraumeni would increase suspicion for malignancy.[4]

Physical examination includes a full head and neck and cranial nerve examination. Nasal endoscopy is also indicated in the majority of cases to identify the extent of the lesion and in surgical planning. Ophthalmological and neurosurgical consultation is also obtained for completion of the preoperative evaluation as indicated by exam findings and radiographic concern for extension into the orbit/intracranial space, respectively, and/or for collaboration for surgical approaches. In the setting of orbital or optic canal involvement, serial ophthalmologic examinations can detect subtle decrement in function and aid in the decision to proceed with surgical intervention. Currently, visual acuity and visual fields are the mainstay of assessment, but newer methods utilizing optical coherence tomography may improve the sensitivity of evaluations and guide interventions in lesions that are observed over time.[6] Dentistry or oral and maxillofacial surgery may also be involved if the disease process extends to the maxillary dentition.

Radiographic evaluation typically includes both CT and MRI. The utility of CT in delineating bony involvement is unsurpassed but the need for evaluation of the impact of the fibro-osseous lesion on the adjacent neural, muscular, and vascular structures necessitates MRI as well. In all patients, especially the pediatric population, serial CT evaluations and the impact of multiple doses of ionizing radiation should be considered and when observing lesions, MRI is the preferred method of the authors and in the available literature.[2]

Differential diagnosis

Fibrous dysplasia-

Overview

Fibrous dysplasia (FD) is characterized by replacement of medullary and cortical bone with sheets of fibro-osseous tissues with intermixed trabecular bone[1-3,7] and is the most common benign condition of the skull.[8] Due to osteoclastic activity within the lesion, the trabecular bone takes on abnormal shapes on histology with characteristic "Chinese character" appearance.[3,9] While 75% of cases of FD demonstrate a monostotic presentation,[9] polyostotic forms of FD are also seen and these can be associated with McCune-Albright syndrome in which polyostotic FD is accompanied by café-au-lait spots and endocrine abnormalities.[10] Of note, FD arising in multiple adjacent cranial bones is considered monostotic.[3] As fibrous dysplasia in all its forms is a somatic mutation,[11] a positive family history is not expected. FD occurs in the head and neck in approximately ¼ of monostotic cases and in up to 50% of polyostotic FD.[2,10] Within the skull base, the sphenoid and ethmoid bones are impacted more frequently than the frontal and maxillary.[8] The pathogenesis of FD and its localized effects are not fully understood, but pathogenesis is mediated by upregulation of the *GNAS1* gene with resultant increased G protein activity and interference in normal osteoblast maturation.[3,10] This genetic alteration, present in approximately 90% of cases of FD, has not been identified in the pathogensis of ossifying fibromas.[12] As such, in cases where differentiating the 2 pathologies is critical and imaging and histology are unclear, genetic testing for *GNAS*1 mutations may offer additional insight.

Though the majority of FD stabilize with skeletal maturity, the slow but unpredictable growth of FD can be problematic for the pediatric patient who presents with this diagnosis. Counseling regarding the expectation of cessation of growth around 18 years for monostotic FD and 22 years for polyostotic FD can be of some solace and help frame discussions regarding interventions.[13] Up to 18% of FD lesions may have persistent activity beyond skeletal maturity,[14] with polyostotic and syndromic lesions having a predilection for this behavior. These data may aid in the decision-making process regarding the appropriateness and timing of more cosmetic recontouring interventions.

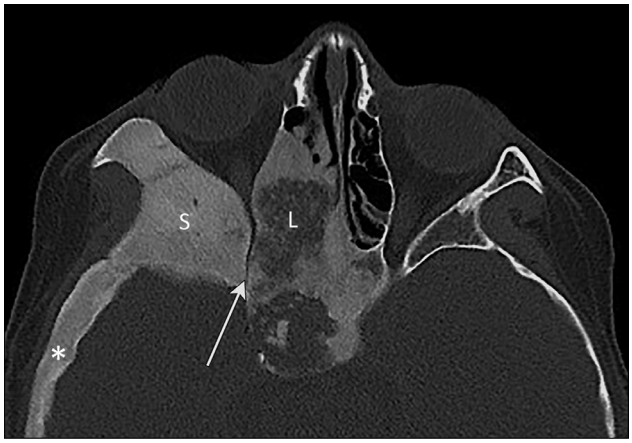

Figure 1 Axial computed tomography (CT) scan of 11-year-old male patient with fibrous dysplasia (FD). The arrow indicates the optic canal that is significantly narrowed. Asterisk highlights the blending of affected bone with surrounding bone, a feature characteristic of FD. The bony CT findings with FD can include both sclerotic (S) and lytic (L) areas. Image courtesy of Jeffrey Rastatter, MD.

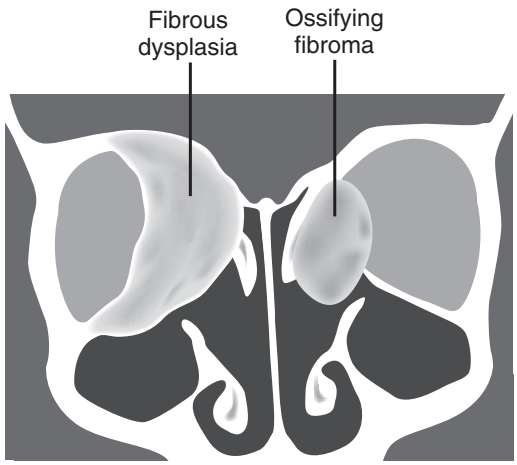

Figure 2 Characteristics of fibrous dysplasia (FD) and ossifying fibroma (OF) that aid in differentiating the 2 on CT. Fibrous dysplasia tends to have ground glass appearance of involved bone with blended borders with surrounding uninvolved bone whereas OF is a well-circumscribed lesion with an irregular, sclerotic border. OF tend to be round or ovoid in shape as well due to their neoplastic expansion from a single focus.

Imaging characteristics

On CT, FD typically demonstrates a “ground glass appearance” of the diploic space with expansion of this space surrounded by thin intact cortical bone (Figure 1).[14,15] The diploic bone can be homogenously sclerotic or lytic but may present with a mixed appearance containing both sclerotic and lytic areas due to variations in osteoblastic activity within the lesion.[2,14,16] FD lesions blend seamlessly with surrounding normal bone,[14,16] a feature that is not usually seen with other fibro-osseous lesions (Figure 2).

On MRI, FD demonstrates low intensity on T2 and low to moderate intensity on T1 sequences with variable enhancement with contrast. As mentioned above, MRI is useful for following FD over time but reliance on MRI alone at the time of diagnosis may result in confusion of FD for a more aggressive malignancy.[2]

Management options

Though FD typically follows an indolent course with presentation in the first 3 decades of life and slow growth after presentation until skeletal maturation,[17] the presence of FD at the skull base represents a potentially problematic scenario in which the orbital contents, cranial neuroforamina, and sinus outflow tract can be compromised. Medical management with bisphosphonate administration has mixed evidence with more recent reports suggesting lack of effect.[2] Radiation is contraindicated in the management of FD due to drastic increase in malignant transformation.[18]

While some advocate for aggressive surgical resection with a goal of total resection in FD,[19] the growing consensus is a symptom-driven approach with a goal of symptom resolution rather than gross total resection (Table 1). Clear indications for intervention include optic or other cranial neuropathy, diplopia, and proptosis.[1,2] In these scenarios, the goal of surgery is to decompress symptomatic neural foramina or debulk intraorbital disease in an effort to restore orbital volume, respectively. Endoscopic techniques are well described in adult series for these purposes and the pediatric body of literature continues to expand.[1,2,4] In the setting of superior orbital involvement or extensive frontal involvement an open or combined approach may be required. Regardless of approach, multidisciplinary teams combining otolaryngology, neurosurgery, and potentially ophthalmology and oral surgery expertise can help to optimize outcomes.[2] Utilization of image guidance is recommended in the approach to all fibro-osseous lesions as the distortion of the normal anatomic landmarks presents significant challenges to the surgeon.

Less clear indications for intervention include pain, cosmetic deformity, and prophylaxis for "impending compression". Pain is not reliably relieved with surgical intervention and regrowth is frequently encountered with need for subsequent intervention.[2] Careful counseling is recommended in these circumstances to clearly define goals of care with the patient and family and to manage expectations regarding the need for revision in the highly likely setting of regrowth.[2] In the setting of narrowed optic canals, the literature supports intervening in the setting of visual symptoms and not based upon perceived threats to vision based on imaging, so therapeutic but not prophylactic intervention is recommended.[2,20,21]

In the setting of FD with no functional impairment, watchful waiting with serial imaging is appropriate. As mentioned above, MRI affords a nonionizing imaging modality to monitor for progression after multimodal imaging with CT and MRI has established the diagnosis. If there is a physically visible portion of the lesion, serial photodocumentation is advocated for identifying subtle alterations over time.[2] Serial ophthalmology examination is also recommended if the lesion involves the orbit or optic canal. If sudden changes are noted in the observation

Table 1 Pediatric skull base fibro-osseous lesions. The etiology, distinctive radiographic findings, indications for intervention, and operative goals are summarized for the most commonly encountered fibro-osseous lesions

Lesion	Etiology	Radiographic pattern on CT	Indication for intervention	Goals of intervention
Fibrous dysplasia	Upregulation of osteoblastic activity through *GNAS1*	Blends with surrounding unaffected bone, usually spares neurovascular foramina, "ground glass" appearance	Impingement with impairment of function, cosmetic deformity	Palliation of symptoms, decompression of neural foramina
Ossifying fibroma	Benign neoplasm	Expansile, often with thick rim of sclerotic bone, well-defined border	Identification	Complete resection
Osteoma	Unknown	Very dense sclerotic, well circumscribed	Functional impairment	Symptom improvement
Aneurysmal bone cyst	Vascular vs neoplastic	Expansile and lytic, can be unicystic or multicystic	Identification	Complete resection
Giant cell tumor	Aggressive benign neoplasm	Expansile and lytic with contrast enhancement	Identification	Complete resection
Osteosarcoma	Malignant Neoplasm	Soft tissue extension beyond bony boundaries with periosteal reaction	Identification	Complete resection

period, this should prompt reimaging with consideration for biopsy, as other fibro-osseous lesions have been noted to arise within FD[22] and FD carries a 0.4% rate of malignant transformation.[4] If planning observation and there is any question regarding the FD diagnosis, this should also prompt consideration for biopsy to confirm pathology given presence of aggressive lesions that may masquerade as FD on imaging such as hyperostotic variant ENB, previously described in the adult literature.[23]

Ossifying fibroma

Overview

Ossifying fibroma (OF) is a benign neoplasm of bone in which hypercellular osteoid strands are deposited in an expansile bony tumor.[24] OF is known by many names including cemento-ossifying fibroma, cementifying fibroma, and juvenile ossifying fibroma. Subtypes include juvenile psammomatoid OF (JPOF) and juvenile trabecular OF (JTOF). As would be anticipated by the nomenclature, the histologic appearances of these subtypes differ from each other and from conventional OF (Figure 3).[3] As would be expected from their titles, JPOF and JTOF typically affect younger patients, with JTOF typically presenting in the first or second decade while JPOF presents in the second or third decade[3] though reports as low as 3 months of age exist.[25] Both subtypes may impact the pediatric cranial base though JPOF impacts the orbit and sinuses more often than JTOF,[25] which most frequently presents in the maxilla.[3,25] As compared to other benign fibro-osseous lesions, juvenile OF is the most aggressive.

Imaging characteristics

On CT, OF can demonstrate the ground glass appearance noted in FD, but the demarcation and growth of the lesion help to differentiate from FD (Figure 2). OF classically has a round to ovoid shape as would be expected with a neoplasm with sharp demarcation of lesion edge from the surrounding normal bone with an irregularly thickened rim of sclerotic bone (Figure 4).[2,3,15,26]

Management options

Complete resection is necessary for management of ossifying fibroma (Table 1). If disease remains, recurrence rates are >30% (Figure 5).[2,3] The main decision in management is optimizing approach to minimize morbidity and maximize the potential for gross total resection.[1] In the pediatric patient, consideration for unerupted dentition, minimizing brain retraction, and minimizing disruption of craniofacial growth centers may also impact the approach and favors less invasive access methods. The endoscopic approach aids in visualization of the cranial base without need for craniotomy or craniofacial resection and, insofar as it facilitates complete resection, offers a less morbid approach than open techniques.

Aneurysmal bone cyst

Overview

Aneurysmal bone cysts (ABC) are expansile osteolytic lesions that arise within bone and comprised of fibrous septae containing osteoclastic giant cells and blood filled pseudocysts.[3,26] More common in the long bones, 5% or fewer ABC present in the craniofacial skeleton with an even smaller proportion impacting the skull base.[3,4] They

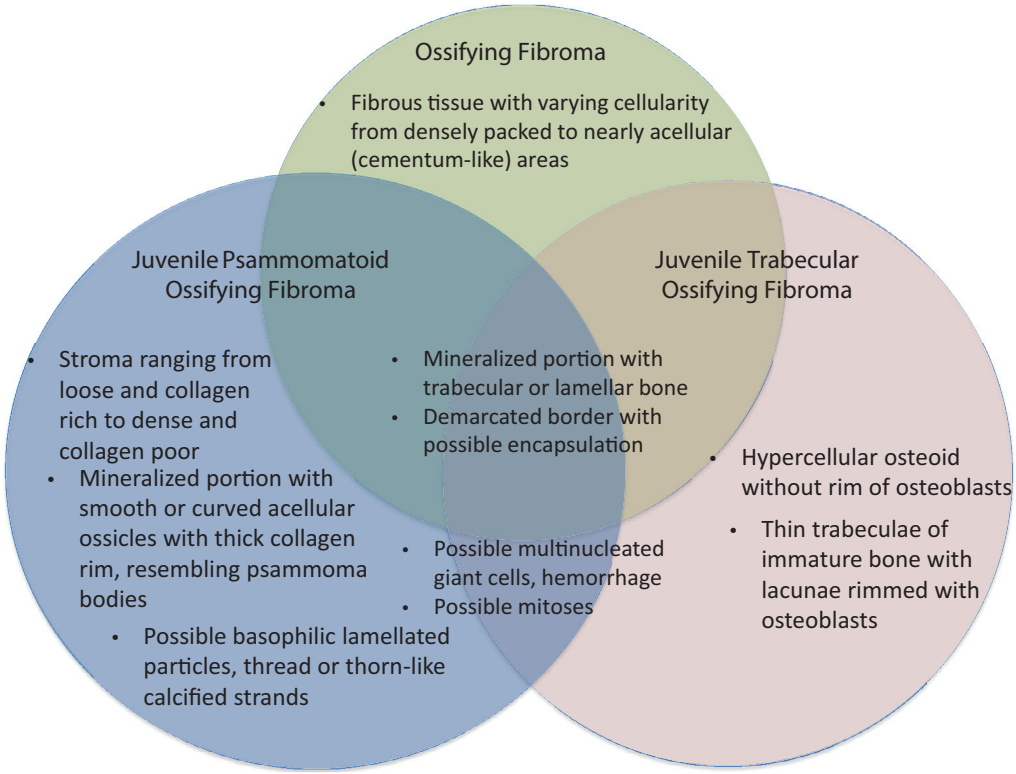

Figure 3 Histopathologic findings characteristic of the varying subtypes of ossifying fibroma. Areas of overlap are shared between the subtypes.

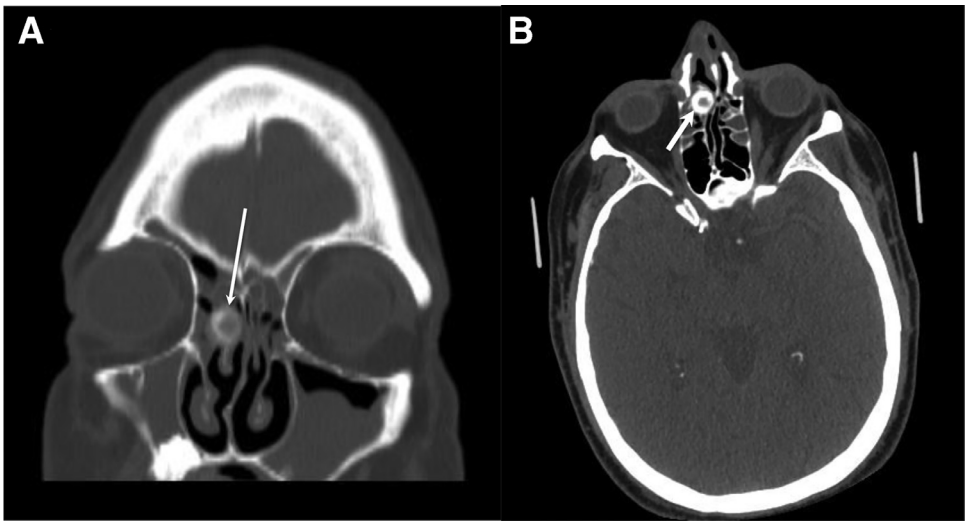

Figure 4 Juvenile ossifying fibroma. On coronal computed tomography (A), the ossifying fibroma is seen abutting the middle turbinate with characteristic ovoid shape (thin arrow). On axial view (B), the sclerotic border is highlighted (thick arrow). Images courtesy of Ricardo Carrau, MD.

present most frequently in the second decade of life.[3] ABC often present in the background of other fibro-osseous lesions and have been seen within FD, OF, and GCT but may also arise de novo.[3,22,25,27-29] Their pathogenesis is not entirely understood, as there is suspected to be contributions from vascular changes within the bone but also seen are several chromosomal rearrangements that suggest a neoplastic process.[3]

Imaging characteristics

ABC are uni- or multicystic and radiolucent centrally with destruction of bone.[4] Borders have a compressive, "pushing" appearance and typically have a thin cortex.[2,26] ABC can extend into adjacent soft tissues through direct spread

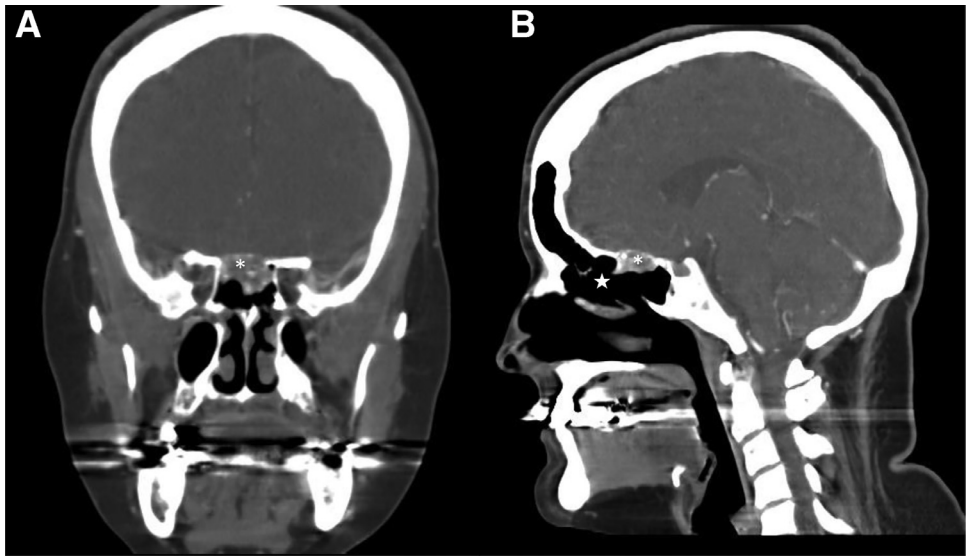

Figure 5 Recurrent ossifying fibroma at the planum sphenoidale. On coronal computed tomography (A) the recurrent disease is noted at the skull base (asterisk). On the sagittal view (B), the lesion is localized to the planum sphenoidale (asterisk). Extensive postoperative changes are also noted (star). Radiographic characteristic findings of OF as in Figure 4 are not identified in this recurrent case. Images courtesy of Ricardo Carrau, MD.

through compromised cortical bone. As such, ABC can appear very aggressive and have been mistaken for chordoma when presenting in the clivus and for other malignant neoplasms when presenting at other skull base locations.[30]

Management options

Complete resection is indicated, as in the case of ossifying fibroma (Table 1). Recurrence risk in the sinonasal region is high with incomplete resection.[29,31,4] This differs from management of ABC in long bones or the mandible, where curettage is often sufficient.[3,4]

Osteoma

Overview

Osteoma are benign bony lesions comprised of cortical bone with minimal fibrous stroma. Found in up to 1% of sinus imaging studies, these represent one of the most common of all sinonasal lesions but are relatively uncommon in the pediatric population.[3,17] Osteoma may be identified incidentally (Figure 6) and are symptomatic indirectly when their growth leads to sinus outflow obstruction, contact with other structures, or orbital symptoms as in Figure 7. Osteoma occur in the frontal, ethmoid, maxillary, and sphenoid sinuses in decreasing frequency and as such can impact the entire cranial base.[26]

Imaging characteristics

Osteoma are extremely radiodense and have clearly defined borders.[3,16] They are homogeneous in their ossification throughout and distort rather than invade adjacent structures.

Management options

Resection is indicated for symptom control but in the setting of asymptomatic incidental findings, osteoma can be observed.[26] In the pediatric patient, clinical observation or MRI would be preferred over serial CT in order to minimize ionizing radiation exposure.

Giant cell tumor of bone

Overview

Giant cells tumors (GCT) are benign but locally aggressive neoplasms of bone with histologic findings of inflammatory multinucleated giant cells intermixed with spindle cells and reactive bone formation.[3] Due to their locally aggressive nature and 1% metastatic potential, the definition of GCT as a highly aggressive benign neoplasm or low grade sarcoma is sometimes questioned.[32] GCT are rare with an overall incidence of 1/1000,000 with a small percentage of these presenting in the skull base and an even smaller subset noted in the pediatric population.[32] The pathogenesis of GCT relates to increased secretion of Receptor Activator of Nuclear Factor Kappa-B-Ligand (RANKL) that serves to increase osteoclastic and giant cell activity.[32]

Imaging characteristics

Due to the osteoclastic activity of the multinucleated giant cells, this is a lytic process.[8] GCT present with expansile lytic, hypodense lesions on CT with minimal ossification.[3] They enhance with contrast on CT.[3] On MRI, GCT tend to be hypointense on T1 images.[3]

Management options

Complete resection is indicated, as in the case of ossifying fibroma (Table 1). Assessment of parathyroid function is

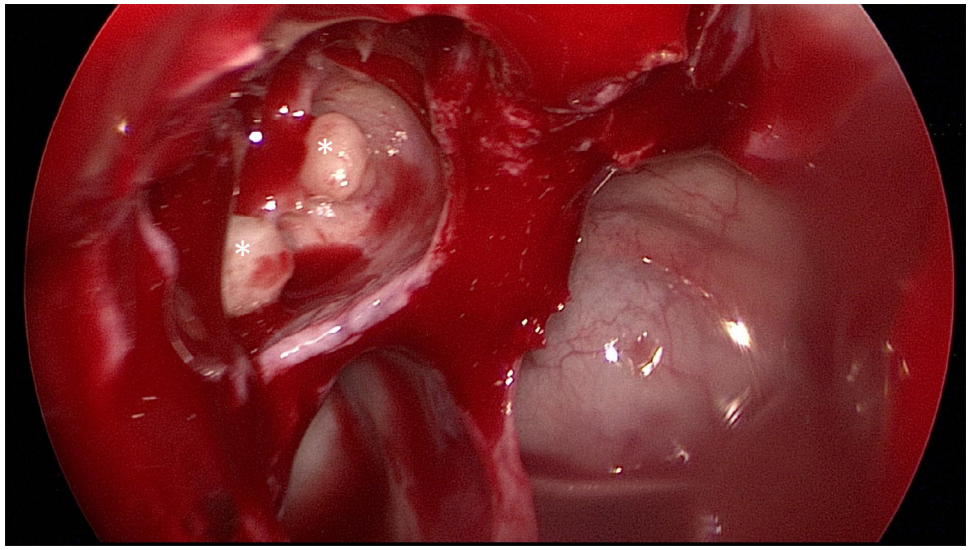

Figure 6 Small sphenoid osteomas (asterisks) identified incidentally during endoscopic skull base surgery. Clinical photo courtesy of Ricardo Carrau, MD.

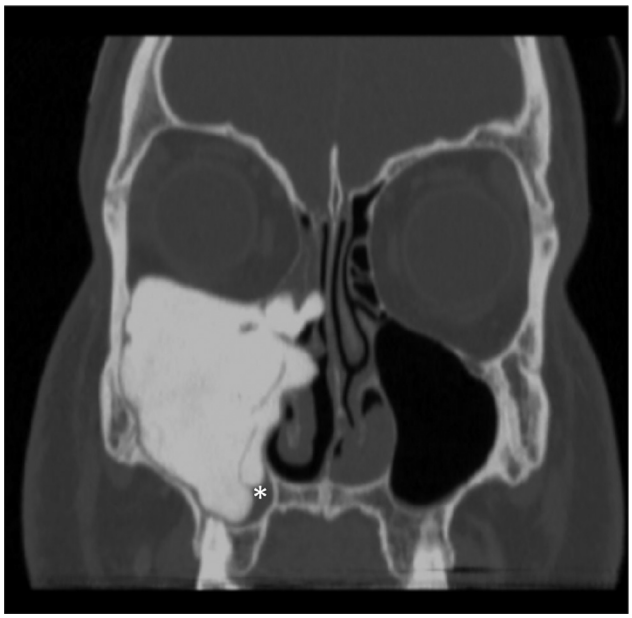

Figure 7 Extensive maxillary osteoma. Note the uniform radiodensity of the lesion and undulating, smooth borders (asterisk). Images courtesy of Ricardo Carrau, MD.

recommended to distinguish GCT from so-called "brown tumor" related to hyperparathyroidism as this can present similarly.[3,17] If complete resection is impossible or excessively morbid, radiotherapy can be considered in GCT[3]. Immunotherapy with denosumab, a monoclonal antibody targeting the RANKL, has also been described.[32] In the setting of unresectable disease, denosumab induction may be considered in order to attempt to reduce the tumor to a resectable state, but recurrence has been noted when therapy is discontinued in the setting of incomplete resection.[32]

Osteosarcoma

Overview

Osteosarcoma is a malignant neoplasm of bone in which unmineralized or poorly mineralized osteoid is deposited by malignant osteoblastic cells in a epithelioid or spindle cell morphology with characteristic features of malignancy including anaplasia and atypical mitoses.[8] It is uncommon in the head and neck in general and especially at the skull base, with only approximately 6% of osteosarcoma cases presenting in the head and neck.[4,5] A history of radiation increases the likelihood for sarcoma, with 10% of osteosarcoma presenting in a radiated field.[3] Mean age of presentation at the cranial base in the pediatric population is 11.6 years in a recent literature review of pediatric osteosarcoma.[33] Of note, an instance of post-traumatic fibro-osseous reparative lesion in the skull base has been reported mimicking the aggressive clinical and radiographic features of osteosarcoma. This entity should be considered in the setting of prior trauma at the site of lesion, but does not rule out osteosarcoma as this has also been reported in the post-traumatic setting.[5,33]

Imaging characteristics

Irregularly bordered with areas of sclerosis and poor mineralization, the CT findings of the osteosarcoma are similar to other fibro-osseous lesions. However, extension beyond the bony boundaries to involve the dura, brain parenchyma, or the extracranial soft tissues is frequently identified[8] and differentiates osteosarcoma from other fibro-osseous lesions other than rare circumstances in which ABC or GCT exhibit soft tissue extension.[4] On CT, a periosteal reaction is also frequently seen.[14]

Management options

Multimodal therapy including gross total resection and adjuvant chemoradiotherapy offers best outcomes.[4,33] In cases initially presenting with unresectable disease, neoadjuvant therapy may also be considered to reduce disease burden to the point of resectability.[33]

Outcomes

With the exception of osteosarcoma which carries a 30% 5-year survival, the remaining fibro-osseous lesions offer favorable outcomes with appropriate treatment. In reported series limited to management of pediatric cranial base fibro-osseous lesions, perioperative complication rates are low in comparison to other skull base lesions though recurrence is not uncommon.[1,2,34] Recurrence varies by pathology and extent of resection achieved. In the setting of FD, where complete resection is not always a feasible or intended goal, progression is seen in up to 25% in remodeling and subtotal resection and 0%-7% in total resection.[19,35] Recurrence rates decrease in monostotic disease and when resection is delayed until after skeletal maturity.[2] Costs of treatment for fibro-osseous lesions is also lower than other cranial base lesions,[34] likely related to less need for ICU stay and shorter overall length of stay due to primarily extradural surgery.

Conclusions

Fibro-osseous lesions of the pediatric cranial base are a heterogenous group of lesions dominated by FD and JOF. Clinical presentation and imaging afford diagnostic evidence that can be used to determine appropriate management plans in the majority of cases. In situations of uncertainty, biopsy can definitively establish the diagnosis. Extent of resection is pathology dependent (Table 1). In the pediatric patient, the endonasal approach affords a minimally invasive technique with less morbidity than open approaches that has been well described generally[34,36,37] and to a lesser extent in the management of fibro-osseous lesions specifically.[1,2,4] In situations where the endonasal approach is not feasible due to disease extension or location, open or combined approaches are utilized, keeping in mind consideration for tooth buds and craniofacial growth centers of particular concern in the pediatric patient. Outcomes in the management of fibro-osseous lesions are generally good, but certain pathologies carry higher risk of recurrence or progression.

Disclosures

None.

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