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El-Mofty Case #1

History: 52 year old woman had left nasal obstruction and epistaxis of several months duration. CT scan showed a soft tissue mass present at the left ethmoid sinus and extends through the medial orbital bone and the floor of the left anterior cranial fossa. A biopsy was performed.

Diagnosis: Glomangiopericytoma (GPC) (Hemangiopericytoma-like tumor).

Glomangiopericytoma is an indolent (benign/borderline malignant) perivascular spindle cell neoplasm with myoid differentiation. It is clinically, morphologically and biologically different from hemangiopericytoma of soft tissue. Phenotypically it is related to perivascular glomus-like myoid cells.

GPC is a rare sinonasal neoplasm usually presents as a nasal mass with unilateral nasal obstruction and epistaxis. It may extend to adjacent paranasal sinuses. There is no gender predilection and it occurs over a wide age range, but most commonly seen in the sixth to the seventh decades. CT scans show opacity with possible bone erosion.

Microscopic examination shows small uniform spindle-shaped cells with indistinct cell borders forming short, interlacing fascicles. There is little interstitial collagen. The vascular patterns are less intricate (staghorn) than in the case of classical HPC. Usually, there is a characteristic perivascular hyalinization. The cell distribution is orderly with rare atypia or mitosis. The tumor cells are immunoreactive for vimentin, smooth muscle actin, muscle-specific actin. Occasionally, they may be positive for CD34 and S100 protein. The cells are however negative for cytokeratin, NSE, and CD31.

The differential diagnosis includes benign and malignant spindle cell neoplasms, including; classical HPC, solitary fibrous tumor, leiomyoma, leiomyosarcoma, spindle cell carcinoma, and spindle cell melanoma.

Surgery is the treatment of choice. The tumor is considered radioresistant. GPC is an indolent neoplasm with local recurrence which may be as high as 30%, usually due to inadequate excision. Recurrence may occur after 1-2 decades. Aggressive behavior (malignant glomangiopericytoma) is rare and is usually associated with large tumor size (>5 CM), invasion, Mitosis (>4/10HPF), necrosis, nuclear atypia and high proliferative index (>20%).

References

Compagno J, Hyams VJ. Hemangiopericytoma-like intranasal tumors. A clinicopathologic study of 23 cases. *Am J Clin Pathol* 1976; 66: 672-683.

Kuo Fy, Lin HC, Evg HL, Huang CC. Sinonasal hemangiopericytoma-like tumor with true pericytic myoid differentiation: a clinicopathologic and immunohistochemical study of five cases. *Head Neck* 2005; 27: 124-129.

Porter PL, Bigler SA, McNutt M, Gown AM. The immunophenotype of hemangiopericytoma and glomus tumor, with special reference to muscle protein expression: an immunohistochemical study and review of the literature. *Mod Pathol* 1991; 4: 46-52.

Thomson LD, Miettinen M, Wenig BM. Sinonasal type hemangiopericytoma: a clinicopathologic and immunophenotypic analysis of 104 cases showing perivascular myoid differentiation. *Am j Surg Pathol* 2003; 27: 737-749.

El-Mofty Case # 2

History: The patient is a 34 year old man who complained of double vision and ptosis of the left eye, of recent onset. Radiographic examination showed an expansive, bone destructive lesion of the clivus which caused a bulge in the sphenoid sinus and posterior nasopharynx. A trans-nasal biopsy was performed.

Diagnosis: Chordoma

Chordoma is a low grade, slow growing, bone-destructive neoplasm of the axial skeleton. It recapitulates the notochord and may arise from its vestigial remnants. It may occur anywhere from the base of the skull and down along the vertebral column. 30% are sphenoid-occipital (cranial).

Cranial chordomas are rare in children. The average age is 35 years as compared to 50 Years for other sites. The male to female ratio is 2:1. Symptoms include: headache, cranial nerves palsy, diplopia, which is common due to VI nerve involvement. The tumors may occasionally present as a nasopharyngeal mass with nasal obstruction. CT scans and MRI show osteolytic lesions with extra-osseous extension. Typically, MRI show low T1 and High T2 weighted signal intensities.

Microscopically, chordomas show a characteristic lobular growth pattern composed of epithelioid to spindle cells dispersed singly or in chords and clusters in a myxoid stroma. Hypercellular as well as hypocellular areas may be present. The cells have abundant eosinophilic cytoplasm that shows vacuolization, which may be intense with soap bubble appearance (physaliphorous cells). Nuclear pleomorphism may be found and mitosis is rare. The tumor cells show positive reactivity to CK, EMA, S100 and vimentin and are negative for MSA, SMA, and Desmin.

Two clinicopathologic variants are known; chondroid chordoma, with variable amounts of cartilage affecting younger patients and has a better prognosis. The other is dedifferentiated chordoma, which has a high grade sarcoma component and a very bad prognosis.

The differential diagnosis of chordoma includes; giant notochordal rests, mucin producing Metastatic carcinomas, myxoid chondrosarcoma, myxoid liposarcoma, and pleomorphic adenoma.

Complete surgical excision is the treatment of choice but because of location in the base of the skull, complete excision is not always possible and recurrence is common. Distant metastasis (7%) may occur

late in the course of the disease. The most commonly affected sites in descending order are the lungs, liver, bone, and lymph nodes

More recently, using proton beam radiation after surgery, the 5 year Disease free survival is 80%. Younger age and chondroid morphology are associated with better outcome. Childhood chordomas, larger tumors, tumor necrosis, dedifferentiated morphology are associated with poor prognosis with 6-12 months overall survival.

References:

Forsyth PA, Cascino TL, Shaw EG, et al. Intracranial chordomas; a clinicopathological and prognostic study of 51 cases. *J Neurosurg* 1993; 78: 741-747.

Hoch BL, Nielson GP, Leibsch NJ, et al. base of the skull chordomas in children and adolescents: a clinicopathologic study of 73 cases. *Am J Surg Pathol* 2006; 30: 811-818.

Pamir MN, Ozduman K. Analysis of radiological features relative to histopathology in 42 skull-base chordomas and chondrosarcomas. *Eur J Radiol* 2006; 53: 461-470.

Meis JM, Raymond AK, Evans HL, et al. "Dedifferentiated" chordoma. A clinicopathologic and immunohistochemical study of three cases. *Am J Surg Pathol* 1987; 11: 516-525.

Wojno KJ, Hruban RH, Garin-Chesa P, et al. Chondroid chordoma and low grade chondrosarcoma of the craniospinal axis. An immunohistochemical analysis of 17 cases. *Am J Surg Pathol* 1992; 16: 1144-1152.

El-Mofty Case # 3

History: 33 Year old man has progressive right facial swelling and nasal obstruction. CT scans showed a 5.5 CM soft tissue mass with areas of calcification centered on the left maxillary sinus, with bone expansion and extension in the medial orbit and right nasal cavity.

Diagnosis: Mesenchymal Chondrosarcoma.

Mesenchymal Chondrosarcoma (MC) is a malignant tumor characterized by a bimorphic pattern composed of highly undifferentiated small round cells and islands of well differentiated hyalin cartilage and often exhibiting a hemangiopericytoma-like vasculature. MC makes up to about 5% of chondrosarcoma.

MC may occur at any age. However, the peak incidence is the second and third decades. Males and females are equally affected. The tumor has a widespread skeletal distribution yet the craniofacial bones, particularly the jaws, are most commonly affected. Extraskelatal involvement may occur in about 25% of the cases, particularly in soft tissue and the meninges. Radiographically the tumor is expansive, lytic and destructive with poor margins. However, some may have well defined margins. Mottled calcifications are sometimes prominent, and extraosseous extension in soft tissues is common.

Microscopically the tumor is characterized by a biphasic pattern, featuring undifferentiated small cells with round dark nuclei, resembling Ewing's sarcoma, with hemangiopericytoma-like vasculature, associated with islands of hyalin cartilage that vary in size and amount of calcification, and may resemble low grade chondrosarcoma. The small cell component, like Ewing/PNET tumor cells, stains positively for Vim, Leu7, and CD99. Cells in the chondroid areas are positive for S100. A few cases of MC demonstrate a chromosomal translocation, $t(11;22)(q24;q12)$, similar to that which occurs in Ewing's sarcoma.

The differential diagnosis of MC includes Ewing/PNET, small cell osteosarcoma and hemangiopericytoma.

The clinical course of MC is variable. Early metastasis and death occur in some cases while others are characterized by protracted course with long term survival. Recurrence and metastasis have occurred more than 10 years and in some cases as long as 20 years, after treatment. Metastasis is commonly to

the lung but also to lymph nodes and bone. 5 year overall survival is 40-50%. 10 year rate is lower. In head and neck cases death due to disease is 35-80%.

References:

Tien N, Chaisuparat R, Fernandes R, et al. Mesenchymal chondrosarcoma of the maxilla: case report and literature review. *J oral Maxillofac Surg* 2007; 65: 1260-1266.

Vencio EF, Reeve CM, Unni KK, et al. Mesenchymal chondrosarcoma of the jaw bones: Clinicopathologic study of 19 cases. *Cancer* 1998; 82: 2350-2355.

Swanson PE, Lillemoe TJ, Manivel JC, et al. Mesenchymal chondrosarcoma. An immunohistochemical study. *Arch Pathol Lab Med* 1990; 114: 943-948.

Granter SR, Renshaw AA, Fletcher CD, et al. CD99 reactivity in mesenchymal chondrosarcoma. *Hum Pathol* 1996; 27: 1273-1276.

Sainati L, Scapinello A, Montaldi A, et al. A mesenchymal chondrosarcoma of a child with the reciprocal translocation (11:22)(q24;q12). *Cancer Genet Cytogenet* 1993;71:144-147.

El-Mofty Case # 4

History: The patient is a 54-year-old man who worked as a wood worker in the furniture business for many years. He complained of right nasal obstruction with sinus pressure and tearing of the right eye of several weeks duration. He was treated with antibiotics for sinusitis without improvement. A CT scan showed a nasal mass involving the ethmoid sinus and extending into the orbit.

Diagnosis: Intestinal-type Adenocarcinoma of the Nose (ITAC)

ITAC is a primary malignant sinonasal neoplasm that bears a close resemblance to adenocarcinoma of the intestines and also to intestinal mucosa, such as villus structures, absorptive cells, goblet cells, Paneth cells, endocrine cells and occasionally muscularis mucosa.

Two clinicopathologic variants of ITAC of the nose are known:

Type 1: Occupational type (O-ITAC)

Type 2: Sporadic type (S-ITAC)

In both types the most common presenting symptom is unilateral nasal obstruction rhinorrhea and epistaxis. Larger lesions are associated with pain, facial swelling, visual and neurologic symptoms. Early lesion may present radiographically as a soft tissue mass with little bone destruction. Other lesions may cause considerable bone damage and invasion of subjacent structures such as the orbit and cranial cavity.

O-ITAC is considerably more common than S-ITAC. Occupational hazards include, wood dust exposure as in the furniture industry (70-500 fold relative risk), leather industry (shoe and boot) and possible flour exposure as in bakers. 80-90% of patients are men with an average age of 58 years. The most common sites are the roof of nose and ethmoid.

Sporadic ITAC are very uncommon. There are no known etiologic factors. Males are equally affected as females. The average age is also 58 years. The common sites of involvement are the nasal wall and maxillary sinus.

Five microscopic types of ITAC are known; papillary, colonic (more common than the other types), mucinous, solid (very rare), and mixed (composed of some or all of the other types). Microscopic subtypes correspond to tumor grade with papillary being the lowest and solid is the highest grade.

The papillary variant is composed of finger-like projections covered with simple or stratified and crowded tall columnar nonciliated cells with minimal atypia. Goblet cells may or may not be present. Glandular invasive elements are usually found. However in-situ cases are also described.

The colonic type shows predominance of tubuloglandular architecture with increased nuclear pleomorphism and mitosis. Tall columnar cells are crowded and may be interspersed with goblet cells, more closely resembling adenocarcinoma of the large intestine. Villi-like intracystic papillary projections may be seen. The mucinous type is characterized by abundant mucinous stroma with clusters of cells, individual glands and scattered signet ring cells. Pools of mucous are separated by thin connective tissue septa.

The majority of tumors are CK7 + (only a minority of cases may be negative, like primary colon adenocarcinoma), CK20 + (also positive in colon cancer), CDX2 + (intestine specific transcription factor usually positive in colon Ca.), and Villin + (intestinal cytoskeleton protein). The neuroendocrine cells are: SYN+ CHR + and may express gastrin, serotonin and somatostatin.

The differential diagnosis includes metastatic GI adenocarcinoma and primary non-intestinal type adenocarcinoma of the nose. ITAC is less likely to be CEA+ than GI metastasis and is more likely to have neuroendocrine cells reactive with SYN and CHR. Surface epithelial dysplasia is consistent with primary ITAC. Clinical evaluation is important to rule out GI primary. Primary nonintestinal type adenocarcinoma of the nose is very rare and tends to be low grade. There are no known occupational or environmental factors. It is composed of well differentiated small glands, lying back to back and consisting of one cell population with no goblet or Paneth cells. The tumors are CK7+, CK20 -, Villin -, CDX2-, SYN- and CHR-.

Complete surgical excision is the treatment of choice. However, repeated local recurrence is common with ultimate invasion of orbit and cranial cavity. Regional and distant metastasis are not common (10-20% and 10-30% respectively). 60% of patients die of their disease usually within 3 years. Survival is related to histologic type and stage of disease.

3 Year Survival by tumor type (79 Cases)

Papillary: 82%

Colonic: 54%

Mucinous: 40%

Solid: 36%

References:

Barnes L. Intestinal type adenocarcinoma of the nasal cavity and pranasal sinuses. *Am J Surg Pathol* 1986; 10; 192-202.

Kleinsasser O, Schroeder H-G. Adenocarcinoma of the inner nose after exposure to wood dust. Morphological findings and relationships between histopathology and clinical behavior in 79 cases. *Arch Otorhinolaryngol* 1988; 245: 1-15.

Urso C, Ninu MB, Franchi A, et al. Intestinal type adenocarcinoma of the sinonasal tract: clinicopathologic study of 18 cases. *Tumori* 1993; 79: 205-210.

Acheson ED, Cowdell RH, Jolles B. Nasal cancer in the furniture and boot and shoe manufacturing industries. *Prev Med* 1976; 5; 295-315.

Kennedy MT, Jordan RCK, Berean KW, et al. Expression pattern of CK7, CK20, CDX-2, and villin in intestinal-type sinonasal adenocarcinoma. *J Clin Pathol* 2004; 57: 932-937.

Resto VA, Krane JF, Faquin WC et al. Immunohistochemical distinction of intestinal-type sinonasal adenocarcinoma from metastatic adenocarcinoma of intestinal origin. *Ann Otol Laryngol* 2006; 115: 59-64.

Skalova A, Cardesa A, Leivio I, et al. Sinonasal tubulopapillary low-grade adenocarcinoma. Histopathological, immunohistochemical and ultrastructural features of a poorly recognized entity. *Virchow Arch* 2003; 443: 152-158.

Eversole Case #1

OLFACTORY NEUROBLASTOMA, ESTHESIONEUROBLASTOMA

The olfactory neuroblastoma (ONB) is a small round blue cell tumor that derives from the olfactory bulb with growth in the nasal cavity roof. Rarely ectopic tumors are seen either intracranially or within a sinus cavity. These tumors present with a lobular growth pattern, the tumor islands being separated from one another by mature fibrous stromal elements, The nuclei show a granular staining pattern (“salt & pepper”) with veil like filmy cytoplasm. Smaller hyperchromatic cells are interspersed. Homer Wright pseudorosettes are seen occasionally consisting of a central core of neurofibrillary material. Flexner-Wintersteiner rosettes seen in adrenal neuroblastoma are rarely seen in ONB. The differential diagnosis includes PNET/Ewings, sinonasal undifferentiated carcinoma (SNUC), small cell carcinoma and neuroendocrine carcinoma. Differentiating one from the other is aided by molecular assays, fluorescent insitu hybridization for translocations, and gene expression utilizing immunohistochemical markers.

Translocations with any degree of specificity have not been found in ONB whereas the PNET/Ewings neoplasms exhibit a consistent and diagnostic t(11:22) translocation. The tumor cells of ONB are positive for the neural markers synaptophysin, chromogranin, neuron specific enolase, neurofilament protein, beta tubulin and microtubule associated protein. An outer sustentacular cell layer surrounding the solid nests is positive for S-100. Simple keratin markers like CK 7, 8 and 19 are absent, a feature that aids in ruling out SNUC which is positive for these epithelial markers.

ONB presents with nasality, obstruction and epistaxis. It represents 2% of all sinonasal tumors and shows a bimodal age peak in the 2nd and 6th decades without sex predilection.

The tumor grows slowly and is visualized by rhinoscopy and MRI where it invades and fills the upper nasal passages and expands and erodes bone. Outcome is based on histopathology and clinical grading. The Hyams histologic grading system classifies tumors into four grades with grade 1 showing minimal pleomorphism, prominent neurofibrillary matrix, presence of HW rosettes, absent mitoses and absent necrosis whereas grade 4 tumors are highly pleomorphic, lack matrix, fail to show rosettes and are associated with necrosis and marked mitotic activity. It is likely that previous studies have included SNUC as a grade 3 or 4 ONB. Clinically, modifications of the Kadish or Dulguerov system are used with

stage 1 or A, confinement to nasal cavity , having 5 year survival over 75%, stage 2 or B, nasal and paranasal sinus involvement about 70% and stage 3 or C, extrasinonasal extension less than 50%.

References:

Mao L, Xia YP, Zhou YN, Dai RL, Yang X, Wang YJ, Duan SJ, Qiao X, Mei YW, Hu B.: Activation of sonic hedgehog signaling pathway in olfactory neuroblastoma. Oncology. 2009;77(3-4):231-43. Epub 2009 Sep 7.

Fragalla H, Weinreb I.: Olfactory neuroblastoma: a review and update. Adv Anat Pathol. 2009 Sep;16(5):322-31.

Wenig BM.: Undifferentiated malignant neoplasms of the sinonasal tract. Arch Pathol Lab Med. 2009 May;133(5):699-712.

Kim JW, Kong IG, Lee CH, Kim DY, Rhee CS, Min YG, Kim CW, Chung JH. Expression of Bcl-2 in olfactory neuroblastoma and its association with chemotherapy and survival. Otolaryngol Head Neck Surg. 2008 Nov;139(5):708-12.

Bourne TD, Bellizzi AM, Stelow EB, Loy AH, Levine PA, Wick MR, Mills SE.: p63 Expression in olfactory neuroblastoma and other small cell tumors of the sinonasal tract. Am J Clin Pathol. 2008 Aug;130(2):213-8.

Wang SL, Li SH, Chen WT, Chai CY.: Absence of Epstein-Barr virus in olfactory neuroblastoma. Pathology. 2007 Dec;39(6):565-6.

Bumm K, Grizzi F, Franceschini B, Koch M, Iro H, Wurm J, Ceva-Grimaldi G, Dimmler A, Cobos E, Dioguardi N, Sinha UK, Kast WM, Chiriva-Internati M.: Sperm protein 17 expression defines 2 subsets of primary esthesioneuroblastoma. Hum Pathol. 2005 Dec;36(12):1289-93.

Mhaweche P, Berczy M, Assaly M, Herrmann F, Bouzourene H, Allal AS, Dulguerov P, Schwaller J.: Human achaete-scute homologue (hASH1) mRNA level as a diagnostic marker to distinguish esthesioneuroblastoma from poorly differentiated tumors arising in the sinonasal tract. Am J Clin Pathol. 2004 Jul;122(1):100-5.

Eversole, Case #2

MIDLINE ANAPLASTIC CARCINOMA WITH NUT REARRANGEMENT

This tumor, arising in a child off the midline of the tongue is characterized by sheets of epithelioid cells that often fail to show contiguous attachments (large anaplastic round cell tumor). The nuclei are large and rhabdoid in appearance with copious eosinophilic cytoplasm. The differential includes large anaplastic T cell lymphoma, anaplastic carcinoma, extrarenal rhabdoid tumor and epithelioid sarcoma. The cell population was positive for cytokeratins and vimentin and negative for most other markers including p63.

Due to the anaplastic nature of the tumor and occurrence during childhood, a midline anaplastic carcinoma with nut gene rearrangement was considered. These tumors are not restricted to children but do tend to arise in midline locations in the head and neck area, particularly the larynx and sinonasal tract. These tumors are primarily anaplastic carcinomas and are positive for p63.. Even when the cell population is undifferentiated, foci of squamous differentiation can be identified. Some published series mention that 10-20% of tumors diagnosed as SNUC are in actuality NUT carcinomas.

A translocation with genetic rearrangement occurs involving the nuclear protein from testis (NUT) on chromosome 15 and bromodomain sequences (BRD4) on chromosome 19. t(15:19). The transcripts generate a fusion protein that favors cell cycling. The diagnosis can be confirmed by employing an antibody to the Nut rearrangement fusion protein that shows nuclear localization. Sequencing and FISH are also useful diagnostic techniques for identifying the translocation.

The young lad in this instance died from disease four months following the diagnosis. This represents the typical outcome of these high grade tumors.

References:

Stelow EB, Bellizzi AM, Taneja K, Mills SE, Legallo RD, Kutok JL, Aster JC, French CA. NUT rearrangement in undifferentiated carcinomas of the upper aerodigestive tract. Am J Surg Pathol. 2008 Jun;32(6):828-34.

Haack H, Johnson LA, Fry CJ, Crosby K, Polakiewicz RD, Stelow EB, Hong SM, Schwartz BE, Cameron MJ, Rubin MA, Chang MC, Aster JC, French CA.: Diagnosis of NUT midline carcinoma using a NUT-specific monoclonal antibody. Am J Surg Pathol. 2009 Jul;33(7):984-91.

French CA, Ramirez CL, Kolmakova J, Hickman TT, Cameron MJ, Thyne ME, Kutok JL, Toretsky JA, Tadavarthy AK, Kees UR, Fletcher JA, Aster JC.: BRD-NUT oncoproteins: a family of closely related nuclear proteins that block epithelial differentiation and maintain the growth of carcinoma cells. Oncogene. 2008 Apr 3;27(15):2237-42. Epub 2007 Oct 15.

French CA, Miyoshi I, Kubonishi I, Grier HE, Perez-Atayde AR, Fletcher JA.: BRD4-NUT fusion oncogene: a novel mechanism in aggressive carcinoma. Cancer Res. 2003 Jan 15;63(2):304-7.

Stelow EB, French CA.: Carcinomas of the upper aerodigestive tract with rearrangement of the nuclear protein of the testis (NUT) gene (NUT midline carcinomas). Adv Anat Pathol. 2009 Mar;16(2):92-6.

Eversole Case #3

ALVEOLAR RHABDOMYOSARCOMA

The alveolar variant of rhabdomyosarcoma (ARM) in the head and neck area is more common in adults and favors the nasopharynx and paranasal sinuses, the sphenoid sinus being more often affected. Since it is quite rare, it may be overlooked when assessing small round blue cell tumors of the sinonasal tract. In this case, the classic alveolar pattern is only evident in focal areas, with more diffuse foci (solid variant) seen in others. The alveolar clusters are made up of round nuclei with a “floating” noncohesive pattern. These nuclei are not pleomorphic, although mitotic figures are present. Sometimes clear cells are present. The differential diagnosis includes olfactory neuroblastoma, SNUC, Ewings/Pnet neuroendocrine tumor, neuroendocrine carcinoma, Merkel cell carcinoma, small round cell carcinoma and lymphoma.

Clinically, ARM grows within the sinonasal air way spaces and may ultimately invade and expand the bony walls and extend cranially or into the orbit. The chief symptoms include nasal obstruction, visual changes, epistaxis and bone enlargement of the face. When a grape like pattern of growth is seen akin to rhabdomyosarcomas of the GU tract, they are then referred to as botryoid variants.

Molecular lesions are evident in both childhood and adult ARM consisting of two specific translocations. These include t(2,13)(q35;q14) and t(1,13)(p36;q14) engendering two different fusion proteins, PAX3-FOXO1 and PAX7-FOXO1 respectively. Children with PAX7-FOXO1 experience an improved prognosis. These molecular lesions are detected by sequencing or FISH. From a diagnostic viewpoint, one should always consider ARM in the differential of small round blue cell tumors of the sinonasal tract and order confirmatory muscle markers by IHC. The cells are positive for desmin as well as muscle specific actin, myoglobin, nuclear MyoD1 and nuclear myogenin

References:

Fyrmpas G, Wurm J, Athanassiadou F, Papageorgiou T, Beck JD, Iro H, Constantinidis J.: Management of paediatric sinonasal rhabdomyosarcoma. *J Laryngol Otol.* 2009;123:990-6. Epub 2009 Apr 27.

Callender TA, Weber RS, Janjan N, Benjamin R, Zaher M, Wolf P, el-Naggar A.: Rhabdomyosarcoma of the nose and paranasal sinuses in adults and children. Otolaryngol Head Neck Surg. 1995;112:252-7.

Ahmed AA, Tsokos M.: Sinonasal rhabdomyosarcoma in children and young adults. Int J Surg Pathol. 2007;15:160-5.

Miettinen M.: From morphological to molecular diagnosis of soft tissue tumors. Adv Exp Med Biol. 2006;587:99-113.

Ganesan P, Thulkar S, Rajan A, Bakhshi S.: Solid variant of alveolar rhabdomyosarcoma mimicking non-Hodgkin lymphoma: case report and review of literature. J Pediatr Hematol Oncol. 2008 ;30:772-4.

Charytonowicz E, Cordon-Cardo C, Matushansky J, Ziman M.: Alveolar rhabdomyosarcoma: is the cell of origin a mesenchymal stem cell? Cancer Lett. 2009 Jul 8;279(2):126-36. Epub 2008 Nov 12.

Parham DM, Ellison DA.: Rhabdomyosarcomas in adults and children: an update. Arch Pathol Lab Med. 2006;130:1454-65

Yasuda T, Perry KD, Nelson M, Bui MM, Nasir A, Goldschmidt R, Gnepp DR, Bridge JA.: Alveolar rhabdomyosarcoma of the head and neck region in older adults: genetic characterization and a review of the literature. Hum Pathol. 2009 Mar;40(3):341-8. Epub 2008 Oct 29.

Eversole, Case #4

ANAPLASTIC PLASMA CELL MYELOMA

Plasma cell malignancies are primarily bone marrow derived neoplasms that manifest multicentric distribution (multiple myeloma). Solitary plasmacytoma is a plasma cell neoplasm that arises in bone or the soft tissues, typically in the sinonasal, nasopharyngeal, oropharyngeal and laryngeal regions. Solitary plasmacytoma of bone or soft tissues progresses to multiple myeloma in 35% of patients within ten years.

In this case, sheets of small round blue cells are seen and importantly are monotonous without an admixture of other leukocytes, a feature of chronic inflammation. The cells show copious cytoplasm and eccentric nuclei yet fail to show the classic “clock face” chromatin margination typical for mature plasma cells making this an “immature” or anaplastic plasma cell myeloma. The anaplastic type is associated with rapid dissemination and poor prognosis. Mitotic figures are also encountered and there is virtually no stroma, except for a network of small vascular channels. Immunoglobulin kappa light chain restriction was seen on IHC with a gamma spike on immunoelectrophoresis. The differential diagnosis includes plasmablastic lymphoma and other plasmacytoid B cell lymphomas. In this case, disseminated lesions were identified in bone with a diagnosis of multiple myeloma.

Clonality is confirmed by immunohistochemistry, immunoglobulin gene rearrangement and by monoclonal spikes on serum immunoelectrophoresis. Clonally expanded cells secrete an immunoglobulin product known as M-component, that is present in both serum and urine. Myeloma variants include 1. nonsecretory type, 2. smoldering myeloma, 3. indolent myeloma and 4. plasma cell leukemia. Clinically, bone pain and lytic lesions in the vertebrae, ribs, skull, pelvis, femur and clavicle are seen and systemic complications include anemia, renal failure, decreased normal Igs with tendency for infection and hypercalcemia. Monoclonal gammopathy of undetermined significance (MGUS) shows positivity of M-component in serum, yet lacks any modicum of neoplasia. Some of these patients will ultimately progress to myeloma

References:

Grogan TM, Van Camp B, Kyle RA, Muller-Hernandez HK, Harris NL: Plasma cell neoplasms In: Tumors of the Haematopoietic and Lymphoid Tissues. WHO Classification of Tumours. IARC Press, Lyon, 2001

Bourantas K: Nonsecretory multiple myeloma. Eur J Haematol 1996;56:109-D,

Kyle RA "Benign" monoclonal gammopathy – after 20 to 35 years of follow-up. Mayo Clin Proc 1993;68:26-36

Alexiou C, Kau RJ, Dietzfelbinger H, Kremer M, Spiess JC, Schratzernstaller B, Arnold W: Extramedullary plasmacytoma: tumor occurrence and therapeutic concepts. Cancer 1999;2305-2314

Creach KM, Foote RL, Neben-Wittich MA, Kyle RA.: Radiotherapy for extramedullary plasmacytoma of the head and neck. Int J Radiat Oncol Biol Phys. 2009 Mar 1;73(3):789-94. Epub 2008 Aug 15.

Liebross RH, Ha, CS, Cox JD, Weber D, Delasalle K, Alexanian R: Clinical course of solitary extramedullary plasmacytoma. Radiother Oncol 1999, 52:245-9 Kumar S.: Multiple myeloma - current issues and controversies. Cancer Treat Rev. 2010 May;36 Suppl 2:S3-11.

Madan S, Kumar S.: Review: extramedullary disease in multiple myeloma. Clin Adv Hematol Oncol. 2009 Dec;7(12):802-4.

Bachar G, Goldstein D, Brown D, Tsang R, Lockwood G, Perez-Ordóñez B, Irish J.: Solitary extramedullary plasmacytoma of the head and neck--long-term outcome analysis of 68 cases. Head Neck. 2008 Aug;30(8):1012-9.

Wright Cases #1 & 2

Juvenile Ossifying Fibroma

Juvenile ossifying fibroma, or juvenile aggressive ossifying fibroma, or juvenile active ossifying fibroma as preferred by others, is a controversial lesion that has evolved as a distinct clinicopathologic entity since the mid to late 1980s. For now, it is subclassified into trabecular and psammomatoid variants based on distinctly different histologic and clinical features. While JOF has been compared and often classified as a variant of the more traditional gnathic cemento-ossifying fibroma, these neoplasms are clinically and histologically distinct. Routine cemento-ossifying fibromas are thought to arise from cells in the periodontal ligament and are classified as odontogenic tumors. JOF on the other hand, arises not uncommonly in extragnathic sites of the craniofacial skeleton, sites that are clearly remote from odontogenic tissues and sites that would preclude an odontogenic origin. JOFs have a marked predilection for, but are not limited to, the first 3 decades of life. They are further distinct from the traditional cemento-ossifying fibromas in that they are infiltrative in their growth pattern and are characterized by a significant recurrence rate following surgical removal.

Juvenile Ossifying Fibroma, Trabecular Variant

Clinical features: JOF,TV has a marked predilection for children and young adults. In the series of 44 cases reported by Makek, 60% were 13 or younger. The thorough review by Eversole and colleagues reported a mean age range between 8.5 and 12 years. There is no gender preference. The neoplasm has a strong predilection for the jaws, with the maxilla being favored, however, in the Makek series, 20% affected the frontal or ethmoid bones. Most neoplasms are characterized by rapid and aggressive growth but patients tend to be asymptomatic. Signs and symptoms are dependent of the bone affected

and jaw expansion is common, but extragnathic involvement can produce epistaxis, nasal obstruction, proptosis and exophthalmos, and rarely, intracranial extension has been documented.

Radiographic features: The radiographic features of both variants are similar. Both are characterized by expansile growth with cortical expansion or perforation. The degree of ossification of the matrix is variable; thus lesions range from radiolucent to more mixed lucent/opaque. Ground glass opacity has been reported as has multilocularity.

Histologic features: JOF, TV is essentially characterized by a spindle cell proliferation of variable cellularity with immature trabecular bone formation. Collagen production is variable, as is cellularity and areas of loosening. Mitoses are not uncommonly found but are rarely numerous. Much of the osteoid is highly immature and woven which usually invites consideration of osteogenic sarcoma in the histologic differential diagnosis. Lamellar bone is rarely found unless residual bone is curetted in the margin of the lesion. Foci of clusters of small numbers of giant cells are characteristic. The neoplasm is infiltrative in its growth pattern. Simple cyst, aneurysmal bone cyst or aneurysmal bone cyst like change is documented in the trabecular variant but not as frequently as in the psammomatoid variant.

Treatment and Prognosis: Treatment and prognosis are hard to document as surgical procedures are not always adequately described. Lesions have been treated with a range of aggressiveness from local surgical removal to wide resection. Maxillary and craniofacial involvement may be clinically more aggressive because of the anatomic nature of the thin bones involved and common extrabony extension. Slootweg reported at least one recurrence in 30% of cases and Makek reported a 58% recurrence. Malignant transformation has not been reported.

Juvenile Ossifying Fibroma, Psammomatoid Variant

JOF, PV shares similarities as well as distinct differences with JOF, TV.

Clinical Features: JOF, PV also has a strong predilection for children and young adults but patients tend to be older. Makek's review of 116 cases revealed 63% in the 5-15 age range. The review by Eversole and colleagues reported a mean age range of 16-33. A case has been reported in a 72 year old patient. The PV shows a distinctly different anatomic distribution with a strong predilection for the paranasal sinuses and orbit. In the Makek review, 62% affected these structures compared to 20% affecting the maxilla and only 7% in the mandible. Genders are affected equally. There are no significant differences between the biologic aggressiveness, signs and symptoms and radiographic features of the two variants.

Histologic features: The histologic features are characterized by a highly cellular stroma with numerous evenly distributed, uniform calcifications often described as ossicles. These have been likened to the psammoma bodies in meningiomas and they range from rounded to irregular and angular. They often have a basophilic center with a peripheral rim of immature newly deposited osteoid resembling a brush border. The stromal cellularity tends to be uniform and the neoplastic cells are short, spindled but occasionally more stellate without significant collagen production or fasciculation. Nuclear morphology is bland and mitoses are rarely encountered. Not uncommonly the walls of "cystic" compartments are seen and this has been described as simple cyst, secondary aneurysmal bone cyst or aneurysmal bone cyst-like changes. This is often accompanied by more rapid growth and expansion.

Cytogenetics: Gene deletions in 2q31-2 and chromosome break points Xq26 and 2q33 have been reported.

Treatment and Prognosis: The PV has been treated similarly to the TV. Makek reported a 56% recurrence rate for the 116 cases he reviewed and the recurrence rate for the 112 cases from the AFIP series was 30%.

References:

Neville BW, Damm DD, Allen CM, Bouquot JE. Oral and Maxillofacial Pathology, 3rd ed. Saunders/Elsevier St Louis, MO, 2005; pp 648-50.

Eversole R, Su L, ElMofty S. Benign fibro-osseous lesions of the craniofacial complex. A review. Head and Neck Pathol 2008; 2:177-202.

Brannon RB, Fowler CB. Benign fibro-osseous lesions: a review of current concepts. Adv Anat Pathol 2001; 8:126-43.

Wright JM. Reactive, dysplastic, and neoplastic conditions of periodontal ligament origin. Periodontology 2000; 21:7-15.

Johnson LC, Yousefi M, Vinh TN et al. Juvenile active ossifying fibroma. Its nature, dynamics and origin. Acta Otolaryngol Suppl. 1991; 488:1-40.

Makek MS. So called "Fibro-osseous lesions" of tumorous origin. J Cranio-Max-Fax Surg 1987;15:154-167.

El-Mofty S. Psammomatoid and trabecular juvenile ossifying fibroma of the craniofacial skeleton: two distinct clinicopathologic entities. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2002; 93:296-304.

Slootweg PJ, El Mofty SK. Ossifying fibroma in Barnes L, Eveson JW, Reichart P, Sidransky D, eds. Pathology and Genetics Head and Neck Tumours. Lyon, France: IARC Press; 2005; pp 319-20.

Slootweg PJ, Panders AK, Koopmans R et al. Juvenile ossifying fibroma. An analysis of 33 cases with emphasis on histopathological aspects. J Oral Pathol Med. 1994; 23:385-9.

Slootweg PJ, Muller H. Juvenile ossifying fibroma. Report of four cases. J Craniomaxillofac Surg. 1990; 18:125-9.

Wenig BM, Ninh TN, Smirniotopoulos JG et al. Aggressive psammomatoid ossifying fibromas of the sinonasal region: a clinicopathologic study of a distinct group of fibro-osseous lesions. Cancer 1995;76:1155-65.

Margo CE, Ragsdale BD, Perman KI et al. Psammomatoid (juvenile) ossifying fibroma of the orbit. Ophthalmology 1985;92:150-9.

Margo CE, Weiss A, Habal MB. Psammomatoid ossifying fibroma. Arch Ophthalmol 1986;104:1347-51.

Slootweg PJ, Panders AK, Nikkels PG. Psammomatoid ossifying fibroma of the paranasal sinuses. An extragnathic variant of cemento-ossifying fibroma. Report of three cases. J Cranio-maxillofac Surg 1993;21:294-7.

Han MH, Chang KH, Lee CH et al. Sinonasal psammomatoid ossifying fibromas: CT and MR manifestations. AJNR Am J Neuroradiol 1991;12:25-30.

Dal Cin P, Sciot R, Fossion E et al. Chromosome abnormalities in cementifying fibroma. *Cancer Genet Cytogenet* 1993;71:170-2

Sawyer JR, Tryka AF, Bell JM et al. Nonrandom chromosome breakpoints at Xq26 and 2q33 characterize cemento-ossifying fibromas of the orbit. *Cancer* 1995;76:1853-9.

Wright Case #3

Craniofacial Fibrous Dysplasia

Fibrous dysplasia (FD) represents a group of developmentally related skeletal disorders characterized by the replacement of the normal intermedullary bone with fibrous connective tissue and variable amounts of poorly mineralized woven trabecular bone arranged with no apparent relationship to function. Traditionally it has been subclassified as monostotic, craniofacial where the process crosses suture lines into adjacent bones, polyostotic if more than one bone is affected, and polyostotic with endocrinopathy (McCune Albright Syndrome) .

FD has now been shown to be due to a postzygotic mutation of the GNAS1 gene (guanine nucleotide-binding protein, α -stimulating activity polypeptide 1), resulting in inappropriate bone maturation and deposition of intermedullary connective tissue with randomly dispersed immature woven bone. There is some evidence that the timing of the mutation determines the clinical extent of the disease. The earliest mutation often involves stem cells that ultimately develop into bone, and cause endocrine hyperfunction, and pigmentation resulting in McCune-Albright syndrome. This is characterized by polyostotic fibrous dysplasia, with café au lait spots, and endocrinopathy. Later mutations occur without endocrine and pigmentation effects and result in polyostotic lesions. The latest mutations, often postnatal, result in single monostotic lesions. Mutations of the GNAS1 gene are postzygotic and FD is not vertically transmitted, with one incredibly rare example reported in the late 1979 by Gorlin.

Clinical features: FD is typically diagnosed during the first two decades of life and over 80% of cases occur as monostotic lesions. The natural history and clinical features of FD are dependent on the bones affected. Long bone involvement tends to be symptomatic and prone to fracture. Craniofacial disease tends to produce expansion and disfigurement and may compress vital structures such as the optic

nerve, resulting in blindness. About a third of cases affect the craniofacial skeleton. Patients are asymptomatic and the lesions produce slowly expanding facial asymmetry. The genders are equally affected but the maxilla is more commonly affected than the mandible. Polyostotic involvement is uncommon and the number of bones affected is highly variable. Polyostotic FD with café au lait spots is known as Jaffe-Lichtenstein syndrome and when endocrinopathy is added, the condition is known as McCune-Albright syndrome (MAS). Cases of MAS occur sporadically. Somatic mosaicism accounts for the clinical diversity of phenotypic expression. Various endocrine organs, particularly the gonads and thyroid, are hyperfunctional, most likely from Gs alpha activation and stimulation of endocrine receptors. Sexual precocity is the most common endocrine dysfunction which is more common in girls. Café au lait spots appear within the first two years of life and their margins tend to be much more irregular than the café au lait spots that characterize neurofibromatosis. Multiple bones are generally affected, most commonly the long bones but facial asymmetry affects about a fourth. Craniofacial morbidity in MAS is associated with overproduction of growth hormone. Some patients experience renal phosphate wasting and hypophosphatemia. Originally thought to be the result of Gs α mutations in the renal proximal tubule, the phosphate wasting has been shown to be secondary to production of a potent phosphaturic agent, FGF-23 produced in the bony lesions. Rarely FD is seen in patients with intramuscular myxomas; known as Mazabraud syndrome.

Radiographic features: While the radiographic features of FD of the extracranial skeleton are highly variable, jaw involvement typically appears as ground glass opacity because of the evenly distributed stroma and bony trabeculae histologically. Early lesions can be more radiolucent. The margins of the lesion typically blend with the surrounding bone. Expansion is commonly observed and maxillary involvement often shows involvement of other craniofacial bones, especially the skull base. Periosteal reactions are typically absent.

Histologic features: FD is the prototypical benign fibro-osseous lesion, but the pattern is variable depending on the duration of the lesion. Early lesions show more intermedullary fibrous cellularity but cytologic atypia and mitoses are absent. Early lesions show smaller immature woven bony trabeculae and some osteoblastic rimming can occasionally be seen. Cellularity and osteoblastic rimming tend to decrease with time and the bone may produce a mosaic pattern histologically. Ultimately some of the bone is remodeled into lamellar bone with can be seen is as many as 50% of craniofacial lesions. The bony trabeculae are often curvilinear, not connected to one another and haphazardly arranged. One of the most characteristic features is the uniformity of trabeculae and stroma throughout the lesion; a feature accounting for its ground glass appearance radiographically. If a margin of normal bone is present, the lesion blends histologically and there is no suggestion of encapsulation or circumscription. FD shows significantly similar features to ossifying fibroma and occasionally cemento-osseous dysplasia. Neither of the latter shows the GNAS1 gene mutation that causes FD, and it has been reported recently that IHC immunoreactivity to osteocalcin was strong diffusely throughout FD but weak in ossifying fibroma. No differences were detected in Runx2 expression.

Treatment and Prognosis: Treatment of FD is individualized to each patient and is based on symptoms, the extent of involvement and functional and cosmetic disability. The lesions in many patients will stabilize and stop growing once skeletal maturity is reach, so treatment decisions are often delayed until the lesion stabilizes. An additional advantage of delaying treatment is that regrowth is more common following surgical intervention in younger patients. Small localized lesions, particularly in the mandible, can be excised, while larger lesions are often just surgically recontoured once they stabilize. Advanced imaging technology has been shown to optimize the surgical management of complex craniofacial involvement. Rarely, lesions progress rapidly with sufficient disfigurement that surgical resection has been employed. Bisphosphonates have shown some efficacy, particularly in symptomatic patients and

those with polyostotic involvement. Radiation treatment is contraindicated because of the risk of radiation induced sarcoma.

References:

- Waldron CA. Fibro-osseous lesions of the jaws. *J Oral Maxillofac Surg* 1993; 828-35.
- Speight PM, Carlos R. Maxillofacial fibro-osseous lesions. *Current Diagnostic Pathology* 2006; 12:1-10.
- Eversole R, Su L, ElMofty S. Benign fibro-osseous lesions of the craniofacial complex. A review. *Head and Neck Pathol* 2008; 2:177-202.
- Brannon RB, Fowler CB. Benign fibro-osseous lesions: a review of current concepts. *Adv Anat Pathol* 2001; 8:126-43.
- Sakamoto A, Oda Y, Iwamoto Y et al. A comparative study of fibrous dysplasia and osteofibrous dysplasia with regard to Gs α mutation at the Arg 201 codon. Polymerase chain reaction-restriction fragment length polymorphism analysis of paraffin-embedded tissues. *J Mol Diag* 2000; 2:67-72.
- Cohen MM. The new bone biology: pathologic, molecular, clinical correlates. *Am J Med Genet* 2006; 140:2646-706.
- Lietman SA, Ding C, Levine MA. A highly sensitive polymerase chain reaction method detects activating mutations of the GNAS gene in peripheral blood cells in McCune-Albright syndrome or isolated fibrous dysplasia. *J Bone Joint Surg Am* 2005; 87:2489-94.
- Weinstein LS, Liu J, Sakamoto A et al. Minireview: GNAS: normal and abnormal functions. *Endocrinology* 2004; 145:5459-64.
- El Deeb M, Waite DE, Gorlin RJ. Congenital monostotic fibrous dysplasia-a new possibly autosomal recessive disorder. *J Oral Surg* 1979; 37:520-5.
- Gorlin RJ, Cohen MM, Hennekam RCM. *Syndromes of the Head and Neck*. Oxford University Press, 2001; pp 335-8.
- Toyosawa S, Yuki M, Kishino M et al. Ossifying fibroma vs fibrous dysplasia of the jaw: molecular and immunological characterization. *Modern Pathol* 2007; 20: 389-96.
- Patel MM, Wilkey JF, Abdelsayed R, et al. Analysis of GNAS mutations in cemento-ossifying fibromas and cemento-osseous dysplasias of the jaws. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2010; 109:739-743.
- Fletcher CDM, Unni KK, Mertens F. *World Health Organization Classification of Tumours. Pathology and Genetics. Tumours of Soft Tissue and Bone*. IARC Press, 2002; pp341-2.
- Liens D, Delmas PD, Meunier PJ. Long-term effects of intravenous pamidronate in fibrous dysplasia of bone. *Lancet* 1994; 343:953-4.

Kos M, Luczak K, Godzinski J et al. Treatment of monostotic fibrous dysplasia with pmidronate. J Craniomaxillofac Surg 2004; 32:10-15

Collins MT. Spectrum and natural history of fibrous dysplasia. J Bone Miner Res 2006; 21:Suppl 2 p99-104.

Murray DJ, Edwards G, Mainprize JG et al. Advanced technology in the management of fibrous dysplasia. J Plast Reconstr Aesthet Surg 2008; 61:906-16.

Collins MT. Spectrum and natural history of fibrous dysplasia of bone. J Bone Miner Res 2006; 21:Suppl2,99-104.

Hart ES, Kelly MH, Brillante B et al. Onset, progression and plateau of skeletal lesions in fibrous dysplasia and the relationship to functional outcome. J Bone Miner Res 2007; 22:1468-74.

Wright Case #4

Cemento-osseous dysplasia (COD)

The cemento-osseous dysplasias represent a spectrum of dysplastic conditions affecting cells in the periodontal ligament and their ability to repair/remodel/regenerate bone and cementum. The PDL, bone and cementum have repair/ regenerative properties and osteoblast and cementoblast precursors can be demonstrated in PDL. There is some evidence that PDL fibroblasts are functionally heterogeneous and stem cells can differentiate into osteoblasts as well as cementoblasts depending on local environmental signals. While the precise underlying signal or molecular defect is unknown, the dysplastic process produces radiographic changes associated with the tooth roots. Because the process is not neoplastic, it does not typically produce expansion or displace teeth and most patients are asymptomatic. Lesions are usually diagnosed from routine radiographs. The anatomic extent of the lesions determines the current classification. Lesions, single but more commonly multiple, and affecting the anterior mandible are known as periapical cemento-osseous dysplasia (PCOD). Isolated lesions affecting sites other than the anterior mandible are known as focal cemento-osseous dysplasia (FCOD). Some patients have multiple lesions affecting numerous sites, often in the maxilla as well as mandible; known as florid cemento-osseous dysplasia (FICOD) .

Clinical features: Because of the strong racial predilection for blacks, COD has a highly variable worldwide distribution. It constitutes the most common fibro-osseous lesion biopsied in the USA, yet in many Asia countries, it is distinctly rare.

PCOD has a strong predilection for blacks, accounting for over 70% of cases. Over 90% are women and most lesions are radiolucent or mixed. Lesions tend to be nonexpansile and small with about a third between 1-3mm and another third between 4-9mm. Patients are typically diagnosed in middle age and

there is a distinct maturational sequence of lesions progressing from radiolucent to radiopaque, although not all lesions mature and complete remodeling and regression has been documented in previously radiolucent, mixed and even opaque lesions. Importantly, all affected teeth are vital as dentists commonly mistake the radiolucent lesions for periapical pathology of pulpal origin.

FCOD was separated from cemento-ossifying fibroma and established as an entity in 1994. Interestingly, 83% of previously diagnosed ossifying fibromas were reclassified as FCOD using the newer criteria. Most patients are diagnosed in the fourth decade at a mean age of 38. Approximately 90% of cases affect females and in the two largest series of cases (n= 221 and 241) 32% and 64% respectively affected blacks. 77-86% of cases occurred in the mandible. Interestingly, in one of the series 38% of patients experienced pain or some expansion.

FICOD has a strong predilection for black females, affecting blacks in almost 90% of US patients. It is typically diagnosed in middle age and most patients are asymptomatic and without expansion, although limited expansion is not unusual. Lesions range from lucent to mixed to opaque and the more opaque lesions often have a peripheral lucent halo. The number of lesions is highly variable and often all four quadrants of the maxilla and mandible are affected. Patients with FICOD often have periapical involvement of their anterior mandible.

Clinically or histologically, simple bone cysts are found to complicate COD. These spaces are not epithelial lined and typically, clinicians will report dropping into an empty space. If they curette the wall of the space, it shows the typical histologic features of COD.

Histologic features: COD is typically a fibro-“osseous” lesion, although admittedly there is great debate regarding the histologic features of cementum if it isn’t attached to the root of a tooth. The stroma is fibroblastic and of variable cellularity. Particularly in early lesions, the stroma is highly vascularized and

there is often erythrocyte extravasation. Early lesions typically have delicate woven bony trabeculae, often with some osteoblastic rimming. Occasionally more rounded calcification, often acellular and resembling cementum are encountered. The stroma typically becomes less cellular and vascular with time with a corresponding increase in the amount of matrix produced. Trabeculae enlarge and often branch producing what has been likened to ginger roots. Mature lamellar bone is not typically seen. Ultimately the matrix becomes characterized by large coalescing masses of sclerotic matrix. Typically in the margin are areas of more cellular connective tissue with smaller calcifications.

There is significant histologic similarity between COD and cemento-ossifying fibroma (COF). While there is no single feature unique to either process, several clinical and histologic features allows separation of the two lesions in most cases. COD, particularly early lesions, tends to curette as multiple reddish-brown hemorrhagic gritty fragments compared to COF which often enucleates as a single mass. COD, particularly towards the more sclerotic end of the spectrum, generally has considerably more matrix than COF. COD tends to be more vascular with erythrocyte extravasation. COF tends to show more osteoblastic rimming and the stroma tends to be less vascular and often storiform.

Treatment and Prognosis: The clinical and radiographic features of PCOD and FICOD are often sufficiently distinctive that a provisional diagnosis can be formulated without biopsy. Lesions of FCOD, particularly when they are radiolucent, often need to be biopsied. COD tends to stabilize, often with sclerotic radiopacity and most patients do not experience many symptoms or bony expansion. The greatest risk is the sclerotic areas tend to be relatively avascular and they don't remodel well if injured and are prone to infection. Once infected, large areas often sequestrate necessitating surgical debridement. Maintaining good oral hygiene and optimal dental care is important to prevent the risk of infection.

References :

- Waldron CA. Fibro-osseous lesions of the jaws. *J Oral Maxillofac Surg* 1993; 828-35.
- Speight PM, Carlos R. Maxillofacial fibro-osseous lesions. *Current Diagnostic Pathology* 2006; 12:1-10.
- Eversole R, Su L, ElMofty S. Benign fibro-osseous lesions of the craniofacial complex. A review. *Head and Neck Pathol* 2008; 2:177-202.
- Brannon RB, Fowler CB. Benign fibro-osseous lesions: a review of current concepts. *Adv Anat Pathol* 2001; 8:126-43.
- Wright JM. Reactive, dysplastic, and neoplastic conditions of periodontal ligament origin. *Periodontology* 2000; 21:7-15.
- Kuru L, Parkar MH, Griffiths GS et al. Flow cytometry analysis of gingival and periodontal ligament cells. *J Dent Res* 1998; 77: 555-64.
- Barkana I, Narayanan AS, Grosskop A et al. Cementum attachment protein enriches putative cementoblastic populations on root surfaces in vitro. *J Dent Res* 2000; 79: 1482-88.
- Bosshardt DD. Are cementoblasts a subpopulation of osteoblasts or a unique phenotype? *J Dent Res* 2005; 84: 390-406.
- Zegarelli EV, Kutscher AH, Napoli N et al. The cementoma. A study of 230 patients with 435 lesions. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1964; 17: 219-224.
- Summerlin D-J, Tomich CE. Focal cemento-osseous dysplasia: A clinicopathologic study of 221 cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1994; 78: 611-20.
- Su L, Weathers DR, Waldron CA. Distinguishing features of focal cemento-osseous dysplasia and cemento-ossifying fibromas. I. A pathologic spectrum of 316 cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1997; 84: 301-9.
- Su L, Weathers DR, Waldron CA. Distinguishing features of focal cemento-osseous dysplasia and cemento-ossifying fibromas. II. Clinical and radiological spectrum of 316 cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1997; 84:540-9.
- Melrose RJ, Abrams AM, Mills BG. Florid osseous dysplasia. A clinical-pathologic study of thirty-four cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1976; 41:62-82.
- Miyauchi M, Ogawa I, Takata T et al. Florid cemento-osseous dysplasia with concomitant simple bone cysts: a case in a Japanese woman. *J Oral Pathol Med* 1995; 24:285-7.
- MacDonald-Jankowski DS. Florid cemento-osseous dysplasia: a systematic review. *Dentomaxillofac Radiol* 2003; 32:141-9.
- Mahomed F, Altini M, Meer S et al. Cemento-osseous dysplasia with associated simple bone cysts. *J Oral Maxillofac Surg* 2005; 63:1549-54.

Patel MM, Wilkey JF, Abdelsayed R, et al. Analysis of GNAS mutations in cemento-ossifying fibromas and cemento-osseous dysplasias of the jaws. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2010; 109:739-743.