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**Orbital Fibrous Dysplasia in an Older Than Average Patient**

**Clinical History:** The patient is a 76 y.o. man who was examined by Dr. Christopher Weller of our Oculoplastic Surgery Service on 3/28/18. The patient had been referred for possible biopsy in the office because of a left supraorbital mass. There was concern that this lesion represented a metastasis from a known lung cancer. He had a history of light perception vision in the right eye secondary to an old retinal vein occlusion that had been treated with PRP. He has a history of mild BDR. There also is a history of an epiretinal membrane in each eye. His Retinal care has been provided by Dr. Ingrid Scott of our Retinal Service.

**Past Medical History:** There was a history of left upper lobectomy in 2011 for lung cancer with no evidence of recurrence to date. He also has a history of type 2 diabetes, emphysema, hypertension, hyperlipidemia, hypothyroidism.

**Allergies:** NKA.

**Ocular Examination:** VA: R: LP; L: 20/25, PH 20/20. There was a 2+ APD right eye. Motility: full. Hertel: 16 R; 14 L with base of 100 with left enophthalmos by “worms eye view”. VF: Normal by confrontation left eye; unable to do right eye. SLE WNL except for bilateral PC IOLs.

**CT Head** (with and without contrast): Expansile lesion in the left lateral wall of the orbit measuring 2.3 x 1.6 x 1.7 cm in vertical, transverse and anteroposterior dimensions with areas of cortical discontinuity in the posterior aspect. Mucosal thickening was noted in the right maxillary sinus. A developmental venous anomaly in the right anterior frontal lobe also was noted. The radiologist suggested that, although there were no images available for direct comparison, an MRI report from 5/9/2002 did not comment on the lesion and, therefore, suggested that the lesion likely represented a metastasis.

**Clinical Course:** Left lateral orbitotomy with bone window and biopsy was performed on 4/16/18 without complication. The mass was in the region of the left orbit/frontal process of the zygoma.

**Histopathology:** Sections displayed vascular and fibroblastic stromal proliferation within the bone marrow space with numerous irregular and curvilinear trabeculae of metaplastic woven bone, arising from the fibrovascular stroma. Definite evidence of osteoblastic rimming is not identified. Mature lamellar bone adjacent to the stroma is present.

**Histopathologic Diagnosis:** Bone, cranium, orbit, left lateral wall, mass, excision: Fibrous dysplasia

**Clinical Course (continued):** On POD #2 the patient was involved in an auto accident on his way to our clinic for his postoperative examination. While he was in the ER following the MVA, Ophthalmology was consulted. Fortunately, there was no injury to the operative site. His vision was good at 20/30; however, there was some postoperative periorbital edema. Unfortunately, during the course of the MVA,he did pour hot coffee on his foot resulting in some skin blistering that initially only required routine wound care and gradually healed. He was last examined by Dr. Weller on 6/6/2018. His condition was stable relative to his lateral orbitotomy.His diabetes is poorly controlled. He will receive ongoing retinal care from Dr. Scott who last examined him on 5/7/2018.

**Discussion:**

A clinical entity consistent with fibrous dysplasia (FD) was first described by von Recklinghausen in 1891.1 The term “ polyostotic fibrous dysplasia” was first used by Liechtenstein in 1938.2 In that paper he credits Dr. Henry L. Jaffe for calling his attention to cases of the disorder. In 1942, Lichtenstein and Jaffe called attention to the multiple patterns of bony involvement in FD.3

Fibrous dysplasia (OMIM#1174800) is characterized by the presence of skeletal lesions in which there is replacement of normal bone by abnormal fibrous tissue within which irregular trabeculae of woven bone are haphazardly arranged.4 There are three typical histopathologic patterns in FD.4 The most common pattern is “Chinese writing” in which the thin bony trabeculae are the characteristic feature. Resorption of the interior of bony trabeculae (dissecting resorption) is see frequently. In the pagetoid pattern, dense sclerotic trabecular bone predominates. Finally, hypercellular FD is characterized by significant amounts of bone as in the pagetoid variant; however, the bony trabeculae are discontinuous and distributed in a very orderly pattern that often contains a parallel arrangement. Bland spindle cells predominate as the background for the bony elements of the lesion.5 Molecular pathology diagnostic techniques are of limited value in this lesion, but may be helpful in unusual cases.5 The main differential diagnosis primarily includes low grade central osteosarcoma, and ossifying fibroma (jaw).5 Cemento-ossifying fibroma and juvenile psammomatoid ossifying fibroma also are considerations.6; 7 8

Based on its skeletal distribution FD can be classified monostotic, which involves a single bone, and polyostotic, which involves multiple bones. With craniofacial involvement, the disease is considered monostotic even if several bones are involved as there is said to be only one disease focus.9 Monostotic FD encompasses 70% to 80% of patients.10 FD may be found in association with McCune-Albright Syndrome MAS) or Mazabraud Syndrome (MS). MAS comprises <5% of patients with FD.11 MAS classically is associated with polyostotic FD accompanied by abnormal skin pigmentation, and precocious puberty.12 Other associated endocrine abnormalities may be hyperthyroidism, growth hormone excess, FGF23-mediated phosphate wasting, and hypercortisolism.12 The Jaffe-Lichtenstein type presents with polyostotic FD with café-au-lait spots, but without precocious puberty.13 Mazabraud Syndrome consists of monostotic or polyostotic FD in association with single or multiple intramuscular myxomas.14; 15 An association between FD and encephalocraniocutaneous lipomatosis, which involves tissues of ectodermal and mesodermal origin such as skin, eye, adipose tissue, and brain, has been reported.16

FD represents 7% of all nonmalignant bone tumors and may progress even after puberty.17; 18; 19

FD has usually been considered a disease of childhood; however, the importance of the disease in adulthood has gained increasing recognition. In a systematic review of 31 reports including 788 cases of FD the mean age at presentation was 24 years and no male patients were observed over the fifth decade.20 The patient we present, therefore, was much older that the majority of FD patients at the time of presentation. The most common presentation in craniofacial FD is with facial asymmetry in 86%, followed by an orbital or facial mass in 60%.9 The most common ocular presenting complaint is blurred vision in 24%, followed by eyelid position abnormalities in 10%.9 The most common ophthalmic complications of FD are visual loss, exophthalmos, dysesthesias in the distribution of the trigeminal nerve, epiphora, headaches, diplopia, visual field defects, and even blindness if the optic canal is involved.21; 22

Radiologically, FD is said to be translucent if fibrous tissue predominates, and has a “ground glass appearance if there is more calcification.23 CT scanning of craniofacial FD demonstrates sclerotic involvement in 50%, and pagetoid findings in 15.6%.9 MRI can be useful in characterizing the internal structure of the FD lesion and in determining the extent of intraosseous and any extraosseous involvement.24 Expanded bone and fibrous tissue within the lesion are characterized by low-to-intermediate signal intensity on T1-weighted images, and have low, intermediate, or high signal intensity on T2-weighted images.24 MRI may also be helpful in distinguishing FD from other fibro-osseous lesions, meningioma, Langerhans’ cell histiocytosis, and Paget’s disease.24

FD is caused by activating mutations of the GNAS gene that encodes the cAMP-regulating transcript stimulatory protein G𝞪s resulting in the up-regulation of Wnt/β-catenin signaling.25 There is activation of adenyl cyclase and dysregulation in cAMP production.26 It has been demonstrated that expression of an active G𝞪s mutation in skeletal stem cells is both sufficient and necessary for FD initiation and maintenance.27 Enhanced G𝞪s signaling and cAMP generation are said to accelerate the osteogenic commitment of the stromal cells; however, they inhibit their further differentiation into osteoblasts thereby resulting in the formation of fibrous dysplastic lesions that, nevertheless, express early osteoblastic markers such as alkaline phosphatase.28 The mutation is located on the q arm of chromosome 20 at position 13.3.26 The mutations are found in early embryonic somatic cells resulting in a somatic mosaic state.27 Lack of inheritance of FD in MAS is attributed to probable embryonic lethality of germ-line transmitted activating GNAS mutations, which are said to only survive through mosaicism.25 Clinical manifestations are related to how small or large the cell mass is during embryogenesis when the mutation occurs, and where in the cell mas the somatic mutation occurs.29 G𝞪s and its coupled receptors, which are known as G protein-coupled receptors (GPCRs), are important in endocrine gland function. Therefore, sporadic, mosaic activating G𝞪s mutations can result in autonomous endocrine gland hormone overproduction, which is associated with MAS.27 One theory as to why FD tends to stabilize (normalization) with increasing age is that there is an age-dependent demise of GNAS-mutated cells in these lesions through apoptosis.30; 31

Malignant transformation is uncommon in FD, which generally is considered a cytologically benign disorder.32 It is said to occur in approximately 1% of cases and was associated with previous radiation therapy in 46% of cases one large series.33 Nevertheless, in a systematic review of 31 reports including 788 cases of FD in which 18% of cases recurred or reactivated no cases of sarcomatous change were found.20 Malignancy is more frequent in polyostotic disease, particularly when associated with MAS or MS, but it may occur even in monostotic fibrous dysplasia.32 Associated malignancies are osteosarcoma, fibrosarcoma, chondrosarcoma, and malignant fibrohistiocytoma.33 Conversely, FD can be confused with an osseous neoplasm.34 In approximately 5% of cases of FD, a lesion may exhibit an aggressive growth pattern simulating malignancy but have benign histopathologic findings.35 It has been suggested that craniofacial lesions, in MAS should be monitored closely, particularly in childhood, to provide early detection of optic nerve compression.36

Rarely, FD has been reported in association with other tumors including a case with atypical lymphoplasmacyte-rich meningioma,37 and one with multiple globoid meningiomas.38 Additionally, other lesions may mimic FD.39

There is considerable discussion regarding the surgical management of FD particularly when there is optic canal involvement.13; 17; 21; 40; 41; 42; 43; 44; 45; 46; 47; 48 In one study, even the authors differed among themselves as to the indications for surgical intervention in these patients.40 Even routine exenteration has been recommended for symptomatic patients.49 There may be greater risk of post-surgical regrowth when FD is associated with the MAS.50 Intravenous bisphosphonate is a current non-surgical treatment for FD aimed at reducing pain and strengthening bone; however, it is hoped that therapy targeted at the abnormal pathways resulting from the genetic defect may hold promise in the future.51 Rapid progression of exophthalmos has been seen in FD complicated by aneurysmal bone cyst, hemorrhage, or mucocele within the dysplastic tissue.43; 52; 53; 54; 55; 56; 57

References:

1.von Recklinghausen FD: Die Fibrose oder deformierende Ostitis, die Osteomalacie und die osteoplastische Carcinose in ihren gegenseitigen Benziehungen: Festschrift Rudolph Virchow zum 13 Oktober 1891. Berlin, George Reimer Verlag, 1891

2.Lichtenstein L: Polyostotic fibrous dysplasia. Arch Surg 36:874-898, 1938

3. Lichtenstein L, Jaffe HL: Fibrous dysplasia of bone. A condition affecting one, several or many bones, the graver cases of which may present abnormal pigmentation of skin, premature sexual development, hyperthyroidism or still other extraskeletal abnormalities. Arch Pathol 33:777-816, 1942

4.Riminucci M, Liu B, Corsi A, et al.: The histopathology of fibrous dysplasia of bone in patients with activating mutations of the Gs alpha gene: site-specific patterns and recurrent histological hallmarks. J Pathol 187:249-258, 1999

5.Puls F, Niblett AJ, Mangham DC: Molecular pathology of bone tumours: diagnostic implications. Histopathology 64:461-476, 2014

6.Hekmatnia A, Ghazavi A, Saboori M, et al.: A case report of cemento-ossifying fibroma presenting as a mass of the ethmoid sinus. J Res Med Sci 16:224-228, 2011

7.Linhares P, Pires E, Carvalho B, Vaz R: Juvenile psammomatoid ossifying fibroma of the orbit and paranasal sinuses. A case report. Acta Neurochir (Wien) 153:1983-1988, 2011

8.Burke AB, Collins MT, Boyce AM: Fibrous dysplasia of bone: craniofacial and dental implications. Oral Dis 23:697-708, 2017

9.Rahman AM, Madge SN, Billing K, et al.: Craniofacial fibrous dysplasia: clinical characteristics and long-term outcomes. Eye (Lond) 23:2175-2181, 2009

10.DiCaprio MR, Enneking WF: Fibrous dysplasia. Pathophysiology, evaluation, and treatment. J Bone Joint Surg Am 87:1848-1864, 2005

11.Chapurlat RD, Orcel P: Fibrous dysplasia of bone and McCune-Albright syndrome. Best Pract Res Clin Rheumatol 22:55-69, 2008

12.Dean L: McCune-Albright Syndrome, in Pratt V, McLeod H, Rubinstein W, et al. (eds): Medical Genetics Summaries. Bethesda (MD), National Center for Biotechnology Information (US), 2012

13.Li J, Li H, Liu X, Han Z: Surgical treatment of polyostotic craniomaxillofacial fibrous dysplasia in adult: a case report and review of the literature. Int J Clin Exp Med 8:16756-16764, 2015

14.Santos CT, Choo CT, Loh AH: Orbital fibrous dysplasia with soft tissue hamartoma--a variant of Mazabraud's syndrome. Orbit 27:207-209, 2008

15.Cox JL, Cushman-Vokoun AM, McGarry SV, Kozel JA: Two cases of Mazabraud syndrome and identification of a GNAS R201H mutation by next-generation sequencing. Virchows Arch 470:589-593, 2017

16.Delfino LN, Fariello G, Quattrocchi CC, et al.: Encephalocraniocutaneous lipomatosis (ECCL): neuroradiological findings in three patients and a new association with fibrous dysplasia. Am J Med Genet A 155a:1690-1696, 2011

17.Frodel JL, Funk G, Boyle J, Richardson M: Management of aggressive midface and orbital fibrous dysplasia. Arch Facial Plast Surg 2:187-195, 2000

18.Yuceer N, Kutluhan A, Bekerecioglu M, et al.: Polyostotic fibrous dysplasia with craniofacial localization presenting with frontal lobe compression in a 14-year-old girl. Acta Neurochir (Wien) 141:203-207, 1999

19.Chanson P, Salenave S, Orcel P: McCune-Albright syndrome in adulthood. Pediatr Endocrinol Rev 4 Suppl 4:453-462, 2007

20.MacDonald-Jankowski D: Fibrous dysplasia: a systematic review. Dentomaxillofac Radiol 38:196-215, 2009

21.Bocca G, de Vries J, Cruysberg JR, et al.: Optic neuropathy in McCune-Albright syndrome: an indication for aggressive treatment. Acta Paediatr 87:599-600, 1998

22.Ricalde P, Horswell BB: Craniofacial fibrous dysplasia of the fronto-orbital region: a case series and literature review. J Oral Maxillofac Surg 59:157-167; discussion 167-158, 2001

23.Saxena RK, Varshney S, Singh J, et al.: Haemorrhagic cystic sino-nasal fibrous dysplasia. Indian J Otolaryngol Head Neck Surg 53:154-157, 2001

24.Faul S, Link J, Behrendt S, Rochels R: MRI features of craniofacial fibrous dysplasia. Orbit 17:125-132, 1998

25.Khan SK, Yadav PS, Elliott G, et al.: Induced Gnas(R201H) expression from the endogenous Gnas locus causes fibrous dysplasia by up-regulating Wnt/beta-catenin signaling. Proc Natl Acad Sci U S A 115:E418-e427, 2018

26.Robinson C, Collins MT, Boyce AM: Fibrous Dysplasia/McCune-Albright Syndrome: Clinical and Translational Perspectives. Curr Osteoporos Rep 14:178-186, 2016

27.Zhao X, Deng P, Iglesias-Bartolome R, et al.: Expression of an active Galphas mutant in skeletal stem cells is sufficient and necessary for fibrous dysplasia initiation and maintenance. Proc Natl Acad Sci U S A 115:E428-e437, 2018

28.Turan S, Bastepe M: GNAS Spectrum of Disorders. Curr Osteoporos Rep 13:146-158, 2015

29.Cohen MM, Jr.: Asymmetry: molecular, biologic, embryopathic, and clinical perspectives. Am J Med Genet 101:292-314, 2001

30.Isobe Y, Takahashi K, Kiso H, et al.: Direct evidence for the age-dependent demise of GNAS-mutated cells in oral fibrous dysplasia. Arch Oral Biol 93:133-140, 2018

31.Kuznetsov SA, Cherman N, Riminucci M, et al.: Age-dependent demise of GNAS-mutated skeletal stem cells and "normalization" of fibrous dysplasia of bone. J Bone Miner Res 23:1731-1740, 2008

32.Qu N, Yao W, Cui X, Zhang H: Malignant transformation in monostotic fibrous dysplasia: clinical features, imaging features, outcomes in 10 patients, and review. Medicine (Baltimore) 94:e369, 2015

33.Ruggieri P, Sim FH, Bond JR, Unni KK: Malignancies in fibrous dysplasia. Cancer 73:1411-1424, 1994

34.Wick MR, McDermott MB, Swanson PE: Proliferative, reparative, and reactive benign bone lesions that may be confused diagnostically with true osseous neoplasms. Semin Diagn Pathol 31:66-88, 2014

35.Martini M, Klausing A, Heim N, et al.: Fibrous dysplasia imitating malignancy. J Craniomaxillofac Surg 46:1313-1319, 2018

36.Utriainen P, Valta H, Bjornsdottir S, et al.: Polyostotic Fibrous Dysplasia With and Without McCune-Albright Syndrome-Clinical Features in a Nordic Pediatric Cohort. Front Endocrinol (Lausanne) 9:96, 2018

37.Ghosal N, Furtado SV, Santosh V, et al.: Co-existing fibrous dysplasia and atypical lymphoplasmacyte-rich meningioma. Neuropathology 27:269-272, 2007

38.Tasar M, Ors F, Yetiser S, et al.: Multiple globoid meningiomas associated with craniomandibular fibrous dysplasia: case report. Clin Imaging 28:20-22, 2004

39.Yoshihara S, Kondo K, Ochi A: Diffuse large B-cell lymphoma in the sphenoid sinus mimicking fibrous dysplasia in CT and MRI. BMJ Case Rep 2014, 2014

40.Satterwhite TS, Wolfe SA: Reply: Fibrous Dysplasia: Management of the Optic Canal. Plast Reconstr Surg 137:1061e-1062e, 2016

41.Acheson JF: Optic nerve disorders: role of canal and nerve sheath decompression surgery. Eye (Lond) 18:1169-1174, 2004

42.Lee AG, Michael CB, Blacklock JB: Ophthalmic manifestations of fibrous dysplasia. Ophthalmology 106:858-859, 1999

43.Edelstein C, Goldberg RA, Rubino G: Unilateral blindness after ipsilateral prophylactic transcranial optic canal decompression for fibrous dysplasia. Am J Ophthalmol 126:469-471, 1998

44.Elwy R, Gokden M, Cai R: Emergency Optic Canal Decompression for Vision Salvage in Fibrous Dysplasia. World Neurosurg 109:134-137, 2018

45.Bequignon E, Cardinne C, Lachiver X, et al.: Craniofacial fibrous dysplasia surgery: a functional approach. Eur Ann Otorhinolaryngol Head Neck Dis 130:215-220, 2013

46.Cruz AA, Constanzi M, de Castro FA, dos Santos AC: Apical involvement with fibrous dysplasia: implications for vision. Ophthal. Plast. Reconstr. Surg 23:450-454, 2007

47.Chen., Y.R., Breidahl., et al.: Optic nerve decompression in fibrous dysplasia: indications, efficacy, and safety. Plastic & Reconstructive Surgery 99:22-30, 1997

48.Becelli R, Perugini M, Cerulli G, et al.: Surgical treatment of fibrous dysplasia of the cranio-maxillo-facial area. Review of the literature and personal experience form 1984 to 1999. Minerva Stomatol 51:293-300, 2002

49.Ferguson BJ: Fibrous dysplasia of the paranasal sinuses. Am J Otolaryngol 15:227-230, 1994

50.Boyce AM, Burke A, Cutler Peck C, et al.: Surgical Management of Polyostotic Craniofacial Fibrous Dysplasia: Long-Term Outcomes and Predictors for Postoperative Regrowth. Plast Reconstr Surg 137:1833-1839, 2016

51.Faruqi T, Dhawan N, Bahl J, et al.: Molecular, phenotypic aspects and therapeutic horizons of rare genetic bone disorders. Biomed Res Int 2014:670842, 2014

52.Yuen VH, Jordan DR, Jabi M, Agbi C: Aneurysmal bone cyst associated with fibrous dysplasia. Ophthal. Plast. Reconstr. Surg 18:471-474, 2002

53.Hunter., J.V., Yokoyama., et al.: Aneurysmal bone cyst of the sphenoid with orbital involvement. British Journal of Ophthalmology 74:505-508, 1990

54.Kurokawa Y, Sohma T, Tsuchita H, et al.: Hemorrhage into fibrous dysplasia following minor head injury--effective decompression for the ophthalmic artery and optic nerve. Surg Neurol 32:421-426, 1989

55.Liakos GM, Walker CB, Carruth JA: Ocular complications in craniofacial fibrous dysplasia. Br J Ophthalmol 63:611-616, 1979

56.Terkawi AS, Al-Qahtani KH, Baksh E, et al.: Fibrous dysplasia and aneurysmal bone cyst of the skull base presenting with blindness: a report of a rare locally aggressive example. Head Neck Oncol 3:15, 2011

57.MacNally SP, Ashida R, Williams TJ, et al.: A case of acute compressive optic neuropathy secondary to aneurysmal bone cyst formation in fibrous dysplasia. Br J Neurosurg 24:705-707, 2010