Selected Giant Cell Rich Lesions of the Temporal Bone

Anthony P. Martinez¹ · Jorge Torres-Mora¹

Received: 1 December 2017 / Accepted: 7 March 2018 / Published online: 1 August 2018
© Springer Science+Business Media, LLC, part of Springer Nature 2018

Abstract

Giant cell rich lesions of the temporal bone encompass a wide spectrum of disease that includes infectious, reactive, and neoplastic processes. When dealing with any lesion that can potentially involve bone, it is important to understand both the clinical presentation and to correlate the histologic findings with the radiologic imaging. This review discusses the clinical, the pathologic features including the differential diagnosis, and the treatment of some of the more commonly encountered giant cell rich entities in this region.

Keywords Temporal bone · Sarcoidosis · Chondroblastoma · Tenosynovial giant cell tumor · Giant cell reparative granuloma · Langerhans cell histiocytosis

Chapter: Giant Cell Rich Lesions of the Temporal Bone

Topic: Langerhan Cell Histiocytosis

Introduction

Langerhans cells histiocytosis (LCH) is a clonal proliferation of immature dendritic cells [1, 2]. In the past, various terminology (eosinophilic granuloma, histiocytosis X, Letter-Siwe syndrome, and Hand-Schuller-Christian) has been used to described Langerhans cell histiocytosis depending on the clinical presentation and sites of involvement [3]. Normal Langerhans cells function as antigen-presenting cells that when activated, can migrate to the lymph nodes and present antigens to naïve T cells [4]. In contrast, the clonal cells of LCH not only lose the ability to migrate from their site of origin but also recruit other inflammatory cells that result in lesion establishment and persistence [4].

Clinical

The incidence of LCH varies depending on the study but ranges from 2.2 to 8.9 cases per million/year [5–7],

primarily affecting individuals in the first three decades, and most commonly involving the bone [8]. A study by Fernandez et al. found that approximately 23% of LCH cases involve the temporal bone [9]. Like other sites of involvement, LCH involving the temporal bone tends to occurs in younger patients, with a significant percentage occurring before 10 years of age [10, 11].

Otorrhea is the most common presenting symptom in LCH of the temporal bone [11]. Other clinical symptoms include bone pain, otitis media or externa, and swelling [4, 7, 9, 10]. The triad of an osteolytic lesion with exophthalmos and diabetes insipidus that was used traditionally to describe Hand-Schuller-Christian disease is seen in less than 10% of cases [10].

On CT, imaging typically reveals a destructive and sharply defined, lytic lesion with “beveled-edges” without surrounding sclerosis [9, 12, 13], and there is often a soft tissue component [9, 14]. On MRI, LCH tends to be hypointense on T1 and intermediate to hyper-intense on T2 [15]. Additionally, MRI tends to be better for evaluating intracranial extension [15].

Pathology

Microscopically, LCH consists of a cellular proliferation of sheets of enlarged, oval mononuclear cells (Langerhan cell histiocytes) characterized by unique reniform or cleaved nuclei with pale cytoplasm (Fig. 1). Mitotic figures may be abundant but atypical mitoses should not be seen.

✉ Anthony P. Martinez
anthonymartinezmd@gmail.com

¹ Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN 55902, USA

Fig. 1 **a** Langerhans cell histiocytosis showing a mix of osteoclast giant cells, larger mononuclear cells and mixed inflammation including eosinophils. **b** Higher power shows the reniform or cleaved nuclei of Langerhans cell histiocytosis that stain with **c** Langerin and **d** CD1a

Interspersed inflammation, characteristically eosinophils but plasma cells and lymphocytes are usually present. Osteoclast-like giant cells are nearly always present and foci of necrosis is common.

Immunohistochemically the cells of LCH stain for CD1a (OKT6), S100 protein, and Langerin (CD207) [4, 5, 16]. Cyclin D1, a target of the MAPK pathway, has recently been shown to be expressed in 39 of 39 (100%) cases of LCH [17].

By electron microscopy, LCH demonstrates the ultrastructural presence of Birbeck granules. These have traditionally been considered the gold standard for diagnosis [4] although Langerin immunostaining has been shown to correlate with presence of Birbeck granules [5, 16]. Cytogenetically, LCH often shows loss of DNA sequences involving several chromosomes including 1p [18]. P53 is overexpressed in LCH, but the mechanism is mostly fully understood and is not the result of a mutation in TP53 [19]. Recently, BRAF V600E mutations have been identified in 57% of LCH [20] and BRAF V600E immunohistochemistry tends to correlate with mutational status [21]. Additionally,

further studies have found mutually exclusive mutations leading to activation of the MAPK pathway in wild-type BRAF [17, 22] with a proposed common pathway of LCH resulting in ERK hyperactivation [17, 20, 22].

Differential Diagnosis

Radiographically, the differential is broad and includes other primarily lytic lesions. Histologically, the differential for LCH typically includes other histiocytic lesions such as Rosai-Dorfman and juvenile xanthogranuloma. Rosai-Dorfman is characterized by enlarged, round histiocytes in contrast to the cleaved, reniform nuclei of LCH and Rosai-Dorfman typically has plasma cells instead of eosinophils. The emperipolesis of Rosai-Dorfman can be highlighted by S100 protein and the lesional cells are negative for CD1a [23]. Like LCH, juvenile xanthogranuloma also tends to occur in a younger age group. Additionally, it can happen in association with LCH and patients are often clinically evaluated for LCH when diagnosed with juvenile xanthogranuloma [4]. The histiocytes of juvenile xanthogranuloma are

typically more lipidized than LCH and there are admixed Touton giant cells. Both lesions can have an eosinophilic infiltrate but the lesional cells of juvenile xanthogranuloma are negative for CD1a and are generally negative for S100 protein [24].

Prognosis/Treatment

LCH is clinically stratified as single or multisystem LCH. Patients with single system LCH generally have a more favorable outcome, a higher chance of spontaneous remission, and an overall survival of 100% [6, 7]. Patients with multisystem LCH have a higher relapse rate and a lower overall survival of around 77% [8].

Treatment varies, but involves chemotherapy either as a monotherapy or surgery with or without chemotherapy. For single system LCH, simple curettage or biopsy is diagnostic and will result in healing in most cases [16]. If there are multifocal bone lesions, then the combination of steroids and vinblastine is most commonly used [16]. For Multisystem LCH, initial induction or “intensive” chemotherapy is given to all patients with the goal of achieving complete resolution of signs and symptoms.

Chapter: Giant Cell Rich Lesions of the Temporal Bone

Topic: Sarcoidosis

Introduction

Sarcoidosis is a systemic granulomatous disease that was first recognized in the late 1800s as livid papillary psoriasis [25]. Although the etiology is unknown, sarcoidosis may represent a spectrum of disorders caused by genetically susceptible hosts to a variety of host factors [26], exposure factors [27, 28], and infectious factors [29–31] that lead to granulomatous inflammation. Sarcoidosis is often a diagnosis of exclusion based on clinical and radiologic findings and the presence of non-caseating epithelioid granulomas in the absence of known granulomagenic agents.

Clinical

The annual disease prevalence of sarcoidosis is 10–40 cases per 100,000 persons [25, 32] with a higher rate in African-Americans [25]. Sarcoidosis commonly affects young adults between 20 and 40 years of age [33] and females are slightly more likely to develop the disease [25, 32, 34].

Sarcoidosis primarily affects the lungs, with pulmonary involvement seen in 90–95% of cases [25, 33]. Skin involvement is seen in around 1/3 of cases and 25% bone

involvement is rare and represents only around 5% of patients with systemic involvement [35]. Temporal bone involvement by sarcoidosis in the literature is rare and has been limited to case reports [35–39].

Clinically, 30–60% of patients with sarcoidosis can be asymptomatic [32]. In the temporal bone, hearing loss can be a presenting symptom [38]. Because a vast majority of patients have pulmonary involvement, systemic symptoms can also be present including coughing, wheezing, and chest pain [25, 32]. Skin manifestations can include erythema nodosum, papules, plaques, and subcutaneous nodules among others [25, 34].

Whereas, the typical radiographic feature of pulmonary sarcoidosis is bilateral hilar lymphadenopathy [32], involvement of the temporal bone can show lytic lesions that sometimes have a sclerotic border [35].

Pathology

Microscopically, sarcoidosis demonstrates the so-called “naked tubercles” which are non-caseating granulomas composed of epithelioid to slightly cleaved cells with abundant pale to eosinophilic cytoplasm (Fig. 2). There is often a subtle rim of lymphocytes or plasma cells [25, 34]. Caseation is usually absent but small foci of necrosis can be present [32]. Inclusion bodies including asteroid (star shaped structures composed of lipoprotein) and Schaumann (laminated calcification composed of calcium carbonate) are often present in the cytoplasm of giant cells [25], and multinucleated Langerhans’ type giant cells can also be seen [33].

Differential Diagnosis

The main differential for sarcoidosis is to rule out infectious causes such as mycobacterial infections, fungal, and spirochetes with appropriate stains. Granulomas caused secondary to non-infectious agents such as beryllium or zirconium [27, 28] can exist so it is important to know the patient’s exposure history. Finally, certain neoplasms processes such as squamous cell carcinoma, and lymphoma can have sarcoid-like granulomas [40].

Treatment/Prognosis

In most cases there is no need for treatment as the disease can resolve spontaneously [25]. Corticosteroids are the most frequently employed treatment [32] and patients with steroid resistant disease have been treated with antimalarial drugs and biologics [25]. Patients with sarcoidosis are at a higher risk for malignancy, including lung cancer and lymphoma [25, 41].

Fig. 2 Sarcoidosis with non-caseating, epithelioid granulomas involving a lymph node (**a**) and between bony trabeculae in a case involving the temporal bone (**b**)

Chapter: Giant Cell Rich Lesions of the Temporal Bone

Topic: Tenosynovial Giant Cell Tumor

Introduction

Tenosynovial giant cell tumor is the most common benign tumor of tendon sheath and synovium [42]. It was first described by Jaffe et al. [43], and it is classified as localized and diffuse types based on growth pattern and clinical behavior [44]. When the diffuse type is exclusively in the joint space it is called pigmented villonodular synovitis [44]. Cases of tenosynovial giant cell tumor involving the temporal bone are thought to arise from the temporal mandible joint (TMJ) with most cases centered on the TMJ and glenoid fossa [45].

Clinical

Less than 60 cases involving the TMJ have been published in the English literature [45, 46]. The true incidence of tenosynovial giant cell tumor involving the temporal bone is unknown in part because many have been diagnosed as chondroblastoma in the past [45, 46]. Most patients are diagnosed in the 3rd to 5th decades [47, 48] and there is no significant sex predilection [45].

The most presenting symptom is hearing loss [45, 47] but others include swelling, pain, fullness, and TMJ type symptoms such as trismus [45, 47–49].

Radiographically, tenosynovial giant cell tumor demonstrates a lytic and expansile lesion with a speculated pattern of erosion at periphery on CT [45], while demonstrating a characteristic hypointense T1 and T2 signal on MRI. The T2 hypointensity is related to magnetic susceptibility

Fig. 3 **a** T1 and **b** T2 coronal MRI of tenosynovial giant cell tumor showing involvement lateral and superior to the right TMJ. There are some T1 and T2 low signal areas suggestive of hemosiderin

effects of iron within the hemosiderin laden lesional cells [45] (Fig. 3).

Pathology

Microscopically, tenosynovial giant cell tumors tend to be circumscribed or nodular. They are composed of multiple cell types: small mononuclear cells, larger plasmacytoid mononuclear cells which are the true lesional cells, osteoclast-like giant cells, and a variable amount of xanthoma cells [50]. The smaller, histiocytoid mononuclear cells are kidney or coffee bean shaped with pale cytoplasm and occasionally grooved nuclei [44, 51, 52]. The larger lesional mononuclear cells consist of round, eccentrically placed nuclei with often retracted eosinophilic cytoplasm with a rim of hemosiderin at the periphery [44] (Fig. 4). In addition to these features, tenosynovial giant cell tumors of the temporal bone can have reactive woven bone and chondroid nodules with dystrophic and lace-like calcification reminiscent of chondroblastoma [45, 46].

Immunohistochemically, the smaller mononuclear cells express CD45, CD68, and CD163 [44]. The larger lesional mononuclear cells are positive for desmin in approximately 45–70% of cases [42, 44], and clusterin should be positive in large lesional mononuclear cells of all cases [44]. Importantly, while the lesional cells express desmin, none should be positive for myogenin, MyoD1, SMA or MSA [42].

Cytogenetically, rearrangements of 1p11-13 that frequently involve the CSF1 gene located at 1p13-21 [44] are found in tenosynovial giant cell tumors. CSF1 encodes macrophage colony stimulating factor, and COL6A3 on

chromosome 2q37 [53] is the common rearrangement partner.

Differential Diagnosis

The main differential diagnosis for tenosynovial giant cell tumors of the temporal bone is chondroblastoma. This is again highlighted by the fact that many tenosynovial giant cell tumors were diagnosed as chondroblastomas in the past [45, 46]. In a case series by Carlson et al., 9 of 11 patients with tenosynovial giant cell tumors were originally diagnosed as chondroblastoma [45]. While both lesions have mononuclear cells and giant cells, the larger epithelioid cells with peripheral cytoplasmic hemosiderin should not be seen in chondroblastoma. Additionally, desmin and clusterin positivity in the larger lesional cells of tenosynovial giant cell tumor should not be seen in chondroblastomas. Most of the mononuclear cells in chondroblastoma are positive for S100 protein whereas the smaller histiocytoid mononuclear cells of tenosynovial giant cell tumor are negative. Interestingly, however, a case series by Oda et al. said the mononuclear cells of the chondroid areas in tenosynovial giant cell tumor stained for S100 protein creating a potential pitfall [46]. So it is important to evaluate staining in non-chondroid areas if using immunostains.

Prognosis/Treatment

Tenosynovial giant cell tumors are locally aggressive lesions that rarely metastasize. Surgical resection remains standard therapy [54]. Two of the largest studies examining surgical

Fig. 4 **a** Low power view of tenosynovial giant cell tumor showing a mix of mononuclear cells and foamy histiocytes. **b** The true lesional cells are the larger, plasmacytoid mononuclear cells with eosinophilic

cytoplasm that can have a rim of hemosiderin. **c** Occasional chondroid nodules mimicking chondroblastoma can be seen. **d** Clusterin staining in the larger mononuclear cells

treatment of tenosynovial giant cell tumors found the risk of recurrence after initial surgery around 20% and risk of local failure 28%, respectively [55, 56]. In addition, Palmerini et al. found that size (<2 cm), female gender and complete macroscopic resection was associated with better control [56], although this can be difficult to achieve around the temporal mandibular joint in order to preserve functional outcome.

Chapter: Giant Cell Rich Lesions of the Temporal Bone

Topic: Chondroblastoma

Introduction

Chondroblastoma is a benign cartilage producing neoplasm composed of (immature) chondroblasts [57] that represents less than 1% of primary bone tumors [50, 58, 59]. It was first

described in Codman [60] as an “epiphyseal chondromatous giant cell tumor” and later renamed chondroblastoma by Jaffe and Lichtenstein [61] to distinguish it from giant cell tumor of bone.

Clinical

Temporal bone chondroblastomas most commonly occur in the 4th and 5th decade [58]. This is slightly older than chondroblastomas of the long bones that tend to occur in the first two decades of life [58, 59, 62]. They are more common in males [58, 62, 63] and the squamous part of the temporal bone is the most common site often with involvement of the sphenoid bone [57].

Hearing loss is the most common presenting symptom. Other symptoms include swelling, otorrhea and facial palsy [57, 64, 65].

Radiographically, chondroblastomas are often lytic with a sclerotic rim [58, 59, 62, 66]. On CT, they can show variable calcification with high attenuation while on MRI, they

can often be heterogeneous with a low to iso-intensity on T1 and hypo-intensity on T2. FDG PET/CT is usually hyper-metabolic [57].

Pathology

Microscopically, chondroblastomas are composed of oval and reniform, mononuclear cells with occasional grooves and slightly eosinophilic cytoplasm. Dystrophic calcification is present in the majority of cases and the calcific deposits produced chondroid nodules with a characteristic lace-like pattern [58, 59, 62] (Fig. 5). Variable amounts of osteoclast giant cells can be seen and secondary aneurysmal bone cyst can be seen in up to 15–30% of chondroblastomas [59, 63].

Immunohistochemically, chondroblastomas stain for S100 protein [59, 67, 68] and SOX9, a transcriptional factor involved in regulating synthesis of type II collagen [69]. Cytokeratin expression such as pancytokeratin [59], AE1/AE3 [70], CK8, and CK18 is often present [71]. CD163 stains the background macrophages and osteoclast giant

cells [70]. Interestingly, DOG1, a calcium activated chloride channel can be positive in the cellular chondroblast areas [70].

More recently, chondroblastomas have been shown to have H3F3B mutations that are located on chromosome 17 [72]. This is in contrast to the H3F3A mutations found in giant cell tumor of bone. An immunohistochemical stain targeting the K36M mutation seen in chondroblastomas may help in difficult cases [73].

Differential Diagnosis

The main histologic differential for temporal bone chondroblastoma is tenosynovial giant cell tumor as many chondroblastomas in the past have now been recognized as tenosynovial giant cell tumors [45, 46]. While both lesions have mononuclear cells and giant cells, the large plasmacytoid or ganglion-like cells of tenosynovial giant cell tumor should not be seen in chondroblastoma. Immunostains may be helpful in difficult cases. Additionally, desmin or clusterin

Fig. 5 Chondroblastoma **a** at low power showing eosinophilic chondroid lobules with sheets of mononuclear cells and **b** osteoclast giant cells. **c** At high power, the mononuclear cells are oval with ample

eosinophilic cytoplasm, occasional nuclear grooves and **d** sometimes the classic pericellular “chicken-wire” calcification can be seen

positivity in the larger lesional cells of tenosynovial giant cell tumor should not be seen in chondroblastomas. Most of the mononuclear cells in chondroblastoma are positive for S100 protein whereas the smaller histiocytoid mononuclear cells of tenosynovial giant cell tumor are negative.

Prognosis/Treatment

Chondroblastomas are benign and rarely metastasize [63]. Surgical curettage is an effective treatment method for most chondroblastomas [58] and this is often done either with bone grafting or packing [74]. The recurrence risk is generally around 10% but the reported literature risk ranges from 10 to 35% [63, 66, 75, 76]. In the head and neck, the recurrence rate is higher and can approach 50% [77]. Radiofrequency ablation is another treatment option with similar or lower recurrence rates than curettage [75, 76].

Chapter: Giant Cell Rich Lesions of the Temporal Bone

Topic: Giant Cell Reparative Granuloma

Introduction

Giant cell reparative granuloma also known as giant cell granuloma is a rare benign but sometimes aggressive osteolytic lesion primarily affecting the gnathic bones [78]. It was first described by Jaffe [79] and later described in the temporal bone by Hirschl and Katz [80].

Clinical

Temporal bone giant cell granuloma is more common in males than females and tends to present at a slightly older age (mean ~30 years) than its gnathic counterpart [81]. Aside from temporal bone involvement, there can also be extension into the TMJ joint and involvement of the sphenoid bone [82]. Symptoms vary but can include hearing loss, otalgia, and dizziness [81–84].

Radiologically, giant cell granulomas will usually show an expansile lesion with thinning of the surrounding bone and bone remodeling on CT [85]. Foci of mineralization can be seen. On MRI, there can be a thick low T1-weighted and T2-weighted signal with a variable central signal [83].

Pathology

Microscopically, giant cell granulomas show a proliferation of spindled and polygonal mononuclear cells with eosinophilic cytoplasm and osteoclast-like giant cells in a hemorrhagic, vascular background (Fig. 6). The lesion may have a lobular architecture with reactive osteoid production [78, 80].

Immunohistochemistry has a limited role in giant cell granulomas but certain immunostains can be employed to help rule out other entities such as the H3F3A G34W immunostain seen in giant cell tumor of bone [86] and the H3F3 K36M immunostain seen in chondroblastoma [73].

There is no characteristic cytogenetic abnormality for giant cell granuloma. Recently, giant cell granulomas of the hands and feet showed USP6 rearrangements [87] suggesting they are better classified as solid aneurysmal bone cysts, but importantly, gnathic giant cell granulomas have not showed USP6 rearrangements [87] indicating morphologically similar but cytogenetically distinct entities.

Differential Diagnosis

The differential diagnosis of temporal bone giant cell granuloma would include aneurysmal bone cyst, giant cell tumor of bone, and a Brown tumor. Aneurysmal bone cyst can show a strikingly similar morphology but should have USP6 rearrangements [88]. Giant cell tumor of bone usually has more evenly distributed osteoclast giant cells with nuclei similar to the nuclei of the mononuclear stromal cells. In difficult cases immunohistochemistry or cytogenetic testing may be helpful. Finally, a Brown tumor can also overlap histologically, but it is associated with hyperparathyroidism so laboratory testing looking at calcium, phosphorus, and PTH levels may be helpful.

Treatment/Prognosis

Surgical resection is the mainstay of treatment for giant cell granuloma [82] and recurrence is seen in up to 20% of cases, often in younger patients [89]. Other therapies including intralesional steroids [81] and calcitonin [90, 91] have been used. More recently, denosumab, a monoclonal antibody that binds to RANKL has been used in gnathic giant cell granulomas [92]. It has yet to be seen if there is any benefit in temporal bone giant cell granulomas.

Fig. 6 **a** Giant cell granuloma showing spindled and polygonal mononuclear cells with eosinophilic cytoplasm and osteoclast-like giant cells in a hemorrhagic, vascular background. **b** At higher power, note

how the nuclei in the osteoclasts differ from the mononuclear cells in contrast to those seen in giant cell tumor of bone

References

1. Yu RC, Chu C, Buluwela L, Chu AC. Clonal proliferation of Langerhans cells in Langerhans cell histiocytosis. *Lancet*. 1994;343(8900):767–8.
2. Willman CL, Busque L, Griffith BB, Favara BE, McClain KL, Duncan MH, et al. Langerhans'-cell histiocytosis (histiocytosis X)--a clonal proliferative disease. *N Engl J Med*. 1994;331(3):154–60.
3. Coppes-Zantinga A, Egeler RM. The Langerhans cell histiocytosis X files revealed. *Br J Haematol*. 2002;116(1):3–9.
4. Hicks J, Flaitz CM. Langerhans cell histiocytosis: current insights in a molecular age with emphasis on clinical oral and maxillo-facial pathology practice. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2005;100(2 Suppl):S42–66.
5. Abba O, Egeler RM, Weitzman S. Langerhans cell histiocytosis: current concepts and treatments. *Cancer Treat Rev*. 2010;36(4):354–9.
6. Stalemark H, Laurencikas E, Karis J, Gavhed D, Fadeel B, Henter JI. Incidence of Langerhans cell histiocytosis in children: a population-based study. *Pediatr Blood Cancer*. 2008;51(1):76–81.
7. Campos MK, Viana MB, de Oliveira BM, Ribeiro DD, Silva CM. Langerhans cell histiocytosis: a 16-year experience. *J Pediatr (Rio J)*. 2007;83(1):79–86.
8. Bernstrand C, Sandstedt B, Ahlstrom L, Henter JI. Long-term follow-up of Langerhans cell histiocytosis: 39 years' experience at a single centre. *Acta Paediatr*. 2005;94(8):1073–84.
9. Fernandez-Latorre F, Menor-Serrano F, Alonso-Charterina S, Arenas-Jimenez J. Langerhans' cell histiocytosis of the temporal bone in pediatric patients: imaging and follow-up. *AJR Am J Roentgenol*. 2000;174(1):217–21.
10. McCaffrey TV, McDonald TJ. Histiocytosis X of the ear and temporal bone: review of 22 cases. *Laryngoscope*. 1979;89(11):1735–42.
11. Modest MC, Garcia JJ, Arndt CS, Carlson ML. Langerhans cell histiocytosis of the temporal bone: a review of 29 cases at a single center. *Laryngoscope*. 2016;126(8):1899–904.
12. Majumder A, Wick CC, Collins R, Booth TN, Isaacson B, Kutz JW. Pediatric Langerhans cell histiocytosis of the lateral skull base. *Int J Pediatr Otorhinolaryngol*. 2017;99:135–40.
13. Ginat DT, Johnson DN, Cipriani NA. Langerhans cell histiocytosis of the temporal bone. *Head Neck Pathol*. 2016;10(2):209–12.
14. Abdel-Aziz M, Rashed M, Khalifa B, Talaat A, Nassar A. Eosinophilic granuloma of the temporal bone in children. *J Craniofac Surg*. 2014;25(3):1076–8.
15. Koch BL. Langerhans histiocytosis of temporal bone: role of magnetic resonance imaging. *Top Magn Reson Imaging*. 2000;11(1):66–74.

16. Haupt R, Minkov M, Astigarraga I, Schafer E, Nanduri V, Jubran R, et al. Langerhans cell histiocytosis (LCH): guidelines for diagnosis, clinical work-up, and treatment for patients till the age of 18 years. *Pediatr Blood Cancer*. 2013;60(2):175–84.
17. Shanmugam V, Craig JW, Hornick JL, Morgan EA, Pinkus GS, Pozdnyakova O. Cyclin D1 Is expressed in neoplastic cells of Langerhans cell histiocytosis but not reactive Langerhans cell proliferations. *Am J Surg Pathol*. 2017;41(10):1390–6.
18. Murakami I, Gogusev J, Fournet JC, Glorion C, Jaubert F. Detection of molecular cytogenetic aberrations in langerhans cell histiocytosis of bone. *Hum Pathol*. 2002;33(5):555–60.
19. Weintraub M, Bhatia KG, Chandra RS, Magrath IT, Ladisch S. p53 expression in Langerhans cell histiocytosis. *J Pediatr Hematol Oncol*. 1998;20(1):12–7.
20. Badalian-Very G, Vergilio JA, Degar BA, MacConaill LE, Brandner B, Calicchio ML, et al. Recurrent BRAF mutations in Langerhans cell histiocytosis. *Blood*. 2010;116(11):1919–23.
21. Roden AC, Hu X, Kip S, Parrilla Castellar ER, Rumilla KM, Vrana JA, et al. BRAF V600E expression in Langerhans cell histiocytosis: clinical and immunohistochemical study on 25 pulmonary and 54 extrapulmonary cases. *Am J Surg Pathol*. 2014;38(4):548–51.
22. Chakraborty R, Hampton OA, Shen X, Simko SJ, Shih A, Abhyankar H, et al. Mutually exclusive recurrent somatic mutations in MAP2K1 and BRAF support a central role for ERK activation in LCH pathogenesis. *Blood*. 2014;124(19):3007–15.
23. Kong YY, Kong JC, Shi DR, Lu HF, Zhu XZ, Wang J, et al. Cutaneous rosai-dorfman disease: a clinical and histopathologic study of 25 cases in China. *Am J Surg Pathol*. 2007;31(3):341–50.
24. Janssen D, Harms D. Juvenile xanthogranuloma in childhood and adolescence: a clinicopathologic study of 129 patients from the kiel pediatric tumor registry. *Am J Surg Pathol*. 2005;29(1):21–8.
25. Ruocco E, Gambardella A, Langella GG, Lo Schiavo A, Ruocco V. Cutaneous sarcoidosis: an intriguing model of immune dysregulation. *Int J Dermatol*. 2015;54(1):1–12.
26. Schurmann M, Lympay PA, Reichel P, Muller-Myhsok B, Wurm K, Schlaak M, et al. Familial sarcoidosis is linked to the major histocompatibility complex region. *Am J Respir Crit Care Med*. 2000;162(3 Pt 1):861–4.
27. Newman LS, Rose CS, Bresnitz EA, Rossman MD, Barnard J, Frederick M, et al. A case control etiologic study of sarcoidosis: environmental and occupational risk factors. *Am J Respir Crit Care Med*. 2004;170(12):1324–30.
28. Cummings MM, Hudgins PC. Chemical constituents of pine pollen and their possible relationship to sarcoidosis. *Am J Med Sci*. 1958;236(3):311–7.
29. Gazouli M, Ikonomopoulos J, Koundourakis A, Bartos M, Pavlik I, Overduin P, et al. Characterization of *Mycobacterium tuberculosis* complex isolates from Greek patients with sarcoidosis by Spoligotyping. *J Clin Microbiol*. 2005;43(9):4858–61.
30. Gazouli M, Ikonomopoulos J, Trigidou R, Foteinou M, Kittas C, Gorgoulis V. Assessment of mycobacterial, propionibacterial, and human herpesvirus 8 DNA in tissues of greek patients with sarcoidosis. *J Clin Microbiol*. 2002;40(8):3060–3.
31. Nishiwaki T, Yoneyama H, Eishi Y, Matsuo N, Tatsumi K, Kimura H, et al. Indigenous pulmonary Propionibacterium acnes primes the host in the development of sarcoid-like pulmonary granulomatosis in mice. *Am J Pathol*. 2004;165(2):631–9.
32. Thomas KW, Hunninghake GW. Sarcoidosis. *JAMA*. 2003;289(24):3300–3.
33. Lazarus A. Sarcoidosis: epidemiology, etiology, pathogenesis, and genetics. *Dis Mon*. 2009;55(11):649–60.
34. Fernandez-Faith E, McDonnell J. Cutaneous sarcoidosis: differential diagnosis. *Clin Dermatol*. 2007;25(3):276–87.
35. Dalley RW, Robertson WD, Nugent RA. Computed tomography of calvarial and petrous bone sarcoidosis. *J Comput Assist Tomogr*. 1987;11(5):884–6.
36. Rootjes PA, Rozemeijer W, Dutilh JC. A patient with sarcoidosis and a cryptococcal infection of the skull. *Med J Aust*. 2016;204(9):353.
37. Scheer M, Rabbels J, Neugebauer J, Cornely OA, Drebbler U, Zoeller JE. Combined intra- and extracranial cryptococcal infection of a 20-year-old patient in right temporal area. *J Oral Maxillofac Surg*. 2011;69(1):222–6.
38. Ng M, Niparko JK. Osseous sarcoidosis presenting as a destructive petrous apex lesion. *Am J Otolaryngol*. 2002;23(4):241–5.
39. Verse T, Pirsig W, Heymer B. A case of sarcoidosis of the mastoid. *Laryngorhinootologie*. 1997;76(5):312–4.
40. Kiess AP, Wang H, Travis WD, Yahalom J. Sarcoid in cancer patients: clinical characteristics and associated disease status. *Sarcoidosis Vasc Diffuse Lung Dis*. 2015;32(3):200–7.
41. Cohen PR, Kurzrock R. Sarcoidosis and malignancy. *Clin Dermatol*. 2007;25(3):326–33.
42. Folpe AL, Weiss SW, Fletcher CD, Gown AM. Tenosynovial giant cell tumors: evidence for a desmin-positive dendritic cell subpopulation. *Mod Pathol*. 1998;11(10):939–44.
43. Jaffe HL, Lichtenstein L, Sutro CJ. Pigmented villonodular synovitis, bursitis, and tenosynovitis. *Arch Pathol Lab Med*. 1941;31:731–65.
44. Boland JM, Folpe AL, Hornick JL, Grogg KL. Clusterin is expressed in normal synoviocytes and in tenosynovial giant cell tumors of localized and diffuse types: diagnostic and histogenetic implications. *Am J Surg Pathol*. 2009;33(8):1225–9.
45. Carlson ML, Osetinsky LM, Alon EE, Inwards CY, Lane JJ, Moore EJ. Tenosynovial giant cell tumors of the temporomandibular joint and lateral skull base: review of 11 cases. *Laryngoscope*. 2016. <https://doi.org/10.1002/lary.26435>
46. Oda Y, Izumi T, Harimaya K, Segawa Y, Ishihara S, Komune S, et al. Pigmented villonodular synovitis with chondroid metaplasia, resembling chondroblastoma of the bone: a report of three cases. *Mod Pathol*. 2007;20(5):545–51.
47. Damodar D, Chan N, Kokot N. Pigmented villonodular synovitis of the temporomandibular joint: case report and review of the literature. *Head Neck*. 2015;37(12):E194–9.
48. Eisig S, Dorfman HD, Cusamano RJ, Kantrowitz AB. Pigmented villonodular synovitis of the temporomandibular joint. Case report and review of the literature. *Oral Surg Oral Med Oral Pathol*. 1992;73(3):328–33.
49. Fisher M, Biddinger P, Folpe AL, McKinnon B. Chondroid tenosynovial giant cell tumor of the temporal bone. *Otol Neurotol*. 2013;34(6):e49–50.
50. Fletcher CDM. WHO classification of tumours of soft tissue and bone. Lyon: IARC Press; 2013.
51. Monaghan H, Salter DM, Al-Nafussi A. Giant cell tumour of tendon sheath (localised nodular tenosynovitis): clinicopathological features of 71 cases. *J Clin Pathol*. 2001;54(5):404–7.
52. Ushijima M, Hashimoto H, Tsuneyoshi M, Enjoji M. Giant cell tumor of the tendon sheath (nodular tenosynovitis). A study of 207 cases to compare the large joint group with the common digit group. *Cancer*. 1986;57(4):875–84.
53. West RB, Rubin BP, Miller MA, Subramanian S, Kaygusuz G, Montgomery K, et al. A landscape effect in tenosynovial giant-cell tumor from activation of CSF1 expression by a translocation in a minority of tumor cells. *Proc Natl Acad Sci U S A*. 2006;103(3):690–5.
54. Brahmi M, Vinceneux A, Cassier PA. Current systemic treatment options for tenosynovial giant cell tumor/pigmented villonodular synovitis: targeting the CSF1/CSF1R axis. *Curr Treat Options Oncol*. 2016;17(2):10.

55. Xie GP, Jiang N, Liang CX, Zeng JC, Chen ZY, Xu Q, et al. Pigmented villonodular synovitis: a retrospective multicenter study of 237 cases. *PLoS ONE*. 2015;10(3):e0121451.
56. Palmerini E, Staals EL, Maki RG, Pengo S, Cioffi A, Gambarotti M, et al. Tenosynovial giant cell tumour/pigmented villonodular synovitis: outcome of 294 patients before the era of kinase inhibitors. *Eur J Cancer*. 2015;51(2):210–7.
57. Park SW, Kim JH, Park JH, Moon KC, Paeng JC, Choi BS, et al. Temporal bone chondroblastoma: imaging characteristics with pathologic correlation. *Head Neck*. 2017. <https://doi.org/10.1002/hed.24880>
58. Dahlin DC, Ivins JC. Benign chondroblastoma. A study of 125 cases. *Cancer*. 1972;30(2):401–13.
59. Edel G, Ueda Y, Nakanishi J, Brinker KH, Roessner A, Blasius S, et al. Chondroblastoma of bone. A clinical, radiological, light and immunohistochemical study. *Virchows Arch A Pathol Anat Histopathol*. 1992;421(4):355–66.
60. Codman EA. The classic: epiphyseal chondromatous giant cell tumors of the upper end of the humerus. *Surg Gynecol Obstet*. 1931;52:543. *Clin Orthop Relat Res*. 2006;450:12–6.
61. Jaffe HL, Lichtenstein L. Benign chondroblastoma of bone: a reinterpretation of the so-called calcifying or chondromatous giant cell tumor. *Am J Pathol*. 1942;18(6):969–91.
62. Schajowicz F, Gallardo H. Epiphyseal chondroblastoma of bone. A clinico-pathological study of sixty-nine cases. *J Bone Joint Surg Br*. 1970;52(2):205–26.
63. Lin PP, Thenappan A, Deavers MT, Lewis VO, Yasko AW. Treatment and prognosis of chondroblastoma. *Clin Orthop Relat Res*. 2005;438:103–9.
64. Demirhan H, Acioglu E, Durna YM, Yigit O, Bozkurt ER, Karagoz Y. Temporal bone localized chondroblastoma. *J Craniofac Surg*. 2015;26(8):e689–90.
65. Yollu U, Ibrahimov M, Aslan M, Yilmaz YZ, Yener M, Karaman E. Chondroblastoma of the temporal bone. *J Craniofac Surg*. 2013;24(4):1495–6.
66. Ramappa AJ, Lee FY, Tang P, Carlson JR, Gebhardt MC, Mankin HJ. Chondroblastoma of bone. *J Bone Joint Surg Am*. 2000;82-A(8):1140–5.
67. Weiss AP, Dorfman HD. S-100 protein in human cartilage lesions. *J Bone Joint Surg Am*. 1986;68(4):521–6.
68. Cocchia D, Lauriola L, Stolfi VM, Tallini G, Michetti F. S-100 antigen labels neoplastic cells in liposarcoma and cartilaginous tumours. *Virchows Arch A Pathol Anat Histopathol*. 1983;402(2):139–45.
69. Konishi E, Nakashima Y, Iwasa Y, Nakao R, Yanagisawa A. Immunohistochemical analysis for Sox9 reveals the cartilaginous character of chondroblastoma and chondromyxoid fibroma of the bone. *Hum Pathol*. 2010;41(2):208–13.
70. Akpalo H, Lange C, Zustin J. Discovered on gastrointestinal stromal tumour 1 (DOG1): a useful immunohistochemical marker for diagnosing chondroblastoma. *Histopathology*. 2012;60(7):1099–106.
71. Bousdras K, O'Donnell P, Vujovic S, Henderson S, Boshoff C, Flanagan AM. Chondroblastomas but not chondromyxoid fibromas express cytokeratins: an unusual presentation of a chondroblastoma in the metaphyseal cortex of the tibia. *Histopathology*. 2007;51(3):414–6.
72. Cleven AH, Hocker S, Briare-de Bruijn I, Suzhai K, Cleton-Jansen AM, Bovee JV. Mutation analysis of H3F3A and H3F3B as a diagnostic tool for giant cell tumor of bone and chondroblastoma. *Am J Surg Pathol*. 2015;39(11):1576–83.
73. Amary MF, Berisha F, Mozela R, Gibbons R, Guttridge A, O'Donnell P, et al. The H3F3 K36M mutant antibody is a sensitive and specific marker for the diagnosis of chondroblastoma. *Histopathology*. 2016;69(1):121–7.
74. Tiefenboeck TM, Stockhammer V, Panotopoulos J, Lang S, Sulzbacher I, Windhager R, et al. Complete local tumor control after curettage of chondroblastoma—a retrospective analysis. *Orthop Traumatol Surg Res*. 2016;102(4):473–8.
75. Xie C, Jeys L, James SL. Radiofrequency ablation of chondroblastoma: long-term clinical and imaging outcomes. *Eur Radiol*. 2015;25(4):1127–34.
76. Mashhour MA, Abdel Rahman M. Lower recurrence rate in chondroblastoma using extended curettage and cryosurgery. *Int Orthop*. 2014;38(5):1019–24.
77. Bertoni F, Unni KK, Beabout JW, Harner SG, Dahlin DC. Chondroblastoma of the skull and facial bones. *Am J Clin Pathol*. 1987;88(1):1–9.
78. El-Naggar AK, Chan JKC, Grandis JR, Takata T, Slootweg PJ. WHO classification of head and neck tumours. Lyon: International Agency for Research on Cancer; 2017.
79. Jaffe HL. Giant-cell reparative granuloma, traumatic bone cyst, and fibrous (fibro-oseous) dysplasia of the jawbones. *Oral Surg Oral Med Oral Pathol*. 1953;6(1):159–75.
80. Hirschl S, Katz A. Giant cell reparative granuloma outside the jaw bone. Diagnostic criteria and review of the literature with the first case described in the temporal bone. *Hum Pathol*. 1974;5(2):171–81.
81. Dimitrakopoulos I, Lazaridis N, Sakellariou P, Asimaki A. Giant-cell granuloma in the temporal bone: a case report and review of the literature. *J Oral Maxillofac Surg*. 2006;64(3):531–6.
82. Ma Y, Liu L, Huang D, Han D, Wang J, Wu W, et al. Diagnosis and treatment of giant cell granuloma of the temporal bone: report of eight cases. *Acta Otolaryngol*. 2012;132(6):657–62.
83. Yu JL, Qu LM, Wang J, Huang HY. Giant cell reparative granuloma in the temporal bone of the skull base: report of two cases. *Skull Base*. 2010;20(6):443–8.
84. Van Buren N, Buchmann L, Gurgel R, Shelton C. Giant cell granuloma of the temporal bone. *Otol Neurotol*. 2014;35(7):e211–2.
85. Nackos JS, Wiggins RH 3rd, Harnsberger HR. CT and MR imaging of giant cell granuloma of the craniofacial bones. *AJNR Am J Neuroradiol*. 2006;27(8):1651–3.
86. Amary F, Berisha F, Ye H, Gupta M, Gutteridge A, Baumhoer D, et al. H3F3A (Histone 3.3) G34W immunohistochemistry: a reliable marker defining benign and malignant giant cell tumor of bone. *Am J Surg Pathol*. 2017;41(8):1059–68.
87. Agaram NP, LeLoarer FV, Zhang L, Hwang S, Athanasian EA, Hameed M, et al. USP6 gene rearrangements occur preferentially in giant cell reparative granulomas of the hands and feet but not in gnathic location. *Hum Pathol*. 2014;45(6):1147–52.
88. Oliveira AM, Perez-Atayde AR, Inwards CY, Medeiros F, Derr V, Hsi BL, et al. USP6 and CDH11 oncogenes identify the neoplastic cell in primary aneurysmal bone cysts and are absent in so-called secondary aneurysmal bone cysts. *Am J Pathol*. 2004;165(5):1773–80.
89. Auclair PL, Cuenin P, Kratochvil FJ, Slater LJ, Ellis GL. A clinical and histomorphologic comparison of the central giant cell granuloma and the giant cell tumor. *Oral Surg Oral Med Oral Pathol*. 1988;66(2):197–208.
90. Bird P, Souter M. Giant cell reparative granuloma of the temporal bone treated with Calcitonin—10 years on. *Otol Neurotol*. 2015;36(7):1296.
91. Wiles AB, Dilustro JF, Moody Antonio SA. Congenital giant cell granuloma of the temporal bone. *Arch Otolaryngol Head Neck Surg*. 2011;137(9):942–6.
92. Bredell M, Rordorf T, Kroiss S, Rucker M, Zweifel DF, Rostetter C. Denosumab as a treatment alternative for central giant cell granuloma: a long-term retrospective cohort study. *J Oral Maxillofac Surg*. 2017. <https://doi.org/10.1016/j.joms.2017.09.013>