Giant Cell Reparative Granuloma of the Orbit Associated with Cherubism

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Purpose: To report a case of cherubism with extensive, bilateral orbital involvement occurring in a 27-year-old woman who had the diagnosis established at the age of 4 years.

Design: Single interventional case report.

Intervention: Ophthalmologic examination and computed tomography were performed. The patient underwent multiple surgical excisions using a bicoronal and transorbital approach. The excised orbital tissues were studied histopathologically.

Results: Computed tomography showed bilateral inferior lateral masses involving the orbital floors and producing marked superior displacement of the orbital contents. The intrinsic expansile bone lesions involved the inferior and lateral orbital walls with apical compression of the optic nerves. Histopathologic examination of the masses revealed scattered giant cells in a fibroblastic stroma containing small vascular channels. The lesion was interpreted as giant cell reparative granuloma.

Conclusions: Giant cell reparative granuloma is an uncommon bone lesion that might involve the orbit. Cherubism should be included in the differential diagnosis of lesions that show the histopathologic features of giant cell reparative granuloma. *Ophthalmology 2003;110:1846–1849 © 2003 by the American Academy of Ophthalmology.*

Cherubism is an uncommon disorder that is inherited as an autosomal dominant pattern and is characterized by the presence of bilateral multiple lesions of the mandible and maxillae.[1] The term "cherubism" was coined by Jones in 1933, because he thought the marked fullness of the jaws and cheeks and the upward displacement of the eyes in these patients resembled the "heavenly ward gaze" and round facies of Renaissance cherubs. Although this lesion was originally considered a form of fibrous dysplasia,[2] cherubism was eventually accepted as a clinicopathologic entity with features identical to giant cell reparative granuloma (GCRG).[3] Bilateral lesions involving the angles of the mandible represent a consistent feature of the disease, but extensive involvement of the jaws and maxilla leading to abnormal dentition is frequently encountered. Ophthalmic manifestations are rare and include proptosis, lower eyelid retraction, and superior globe displacement.[4] We believe the proptosis, in our case, is due to the intrinsic bone lesions of GCRG.

To our knowledge only four patients with orbital involvement in cherubism have been documented histopathologically.[4–6] At least seven mutations of the SH3-binding protein SH3BP2 on chromosome 4p16.3 have been described in cherubism.[7]

This report documents a case of cherubism occurring in a 27-year-old woman who had severe bilateral orbital manifestations caused by GCRG. We discuss the clinical and histopathologic criteria of GCRG of the orbit occurring in a patient with cherubism.

Case Report

A 27-year-old-woman, in otherwise good health, complained of incapacitating, progressive diplopia of 18 months' duration. External examination revealed full cheeks and jaw, marked mongoloid palpebral slant, and inferior scleral show and upward deviation of the eyes (Fig 1). Best-corrected visual acuity was 20/25-2 in the right eye and 20/20 in the left eye (decreased from 20/15 in both eyes 4 years earlier). Color vision (Farnsworth D-15) and pupil examinations were normal in both eyes, but there was decreased contrast sensitivity in the right eye. No abnormalities were noted in the optic discs, but there was wrinkling of the internal limiting membranes in each fundus. Automated perimetry demonstrated bilateral superonasal defects. Right hypertropia with an "A" pattern esotropia, bilateral superior oblique overaction, bilateral inferior oblique under action, and an incyclotorsion greater than 35° in primary gaze was found.

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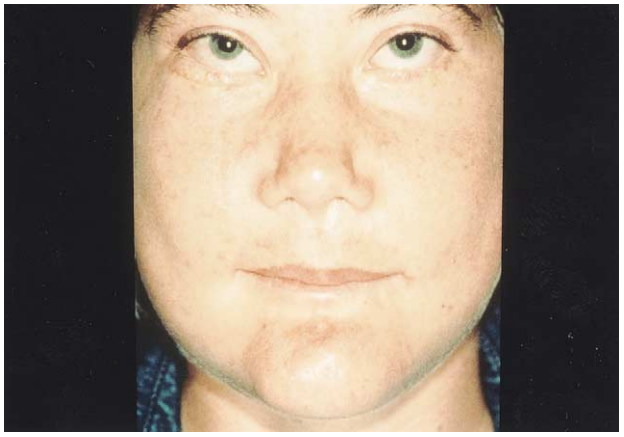

Figure 1. The patient's face shows bilateral fullness of the maxillae and upward deviation of the eyes (cherubic facies) associated with prominent prognathism.

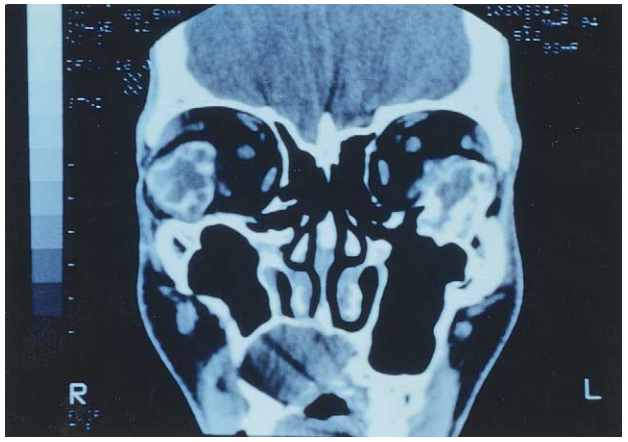

Figure 2. Coronal view of computed tomography depicting well-circumscribed bilateral symmetric extraconal lobulated bony masses displacing the inferior and lateral recti muscles.

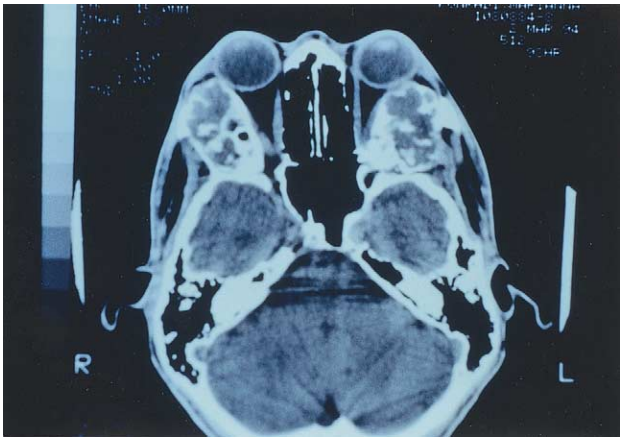

Figure 3. Computed tomography (axial view) displaying oval well-circumscribed bilateral orbital masses with peripheral bone sclerosis and more hypodense areas centrally.

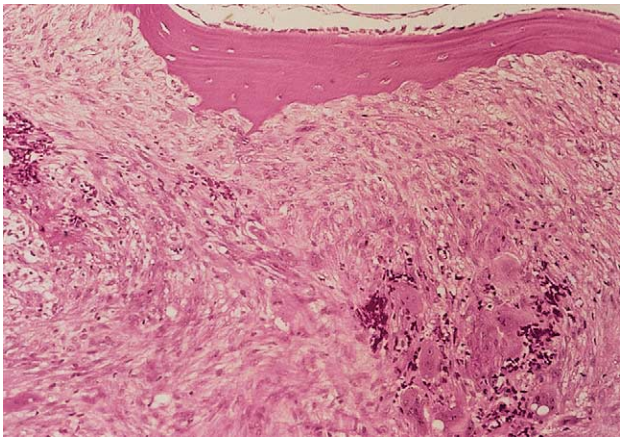

Figure 4. The tumor shows an admixture of spindle-shaped fibroblast-like cells with scattered multinucleated giant cells and foci of hemorrhage. The bony trabecula (shown above) displays a ragged irregular surface lined by osteoclastic giant cells inferiorly and prominent osteoblastic rimming along its superior margin (stain, hematoxylin–eosin; original magnification, ×40).

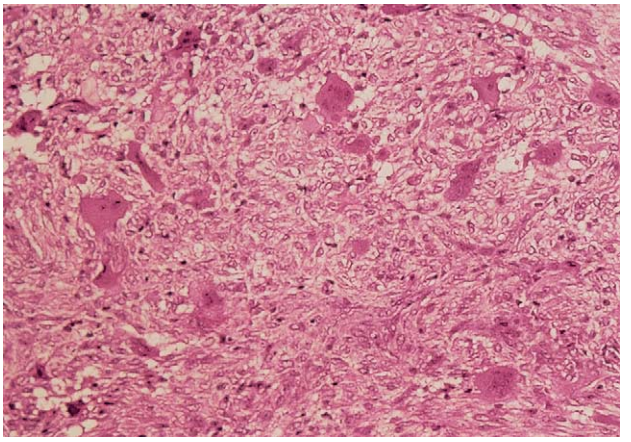

Figure 5. The stroma of the tumor is well vascularized and contains spindle-shaped cells with round to oval nuclei intermixed with many multinucleated giant cells of variable size and shape (stain, hematoxylin–eosin; original magnification, ×64).

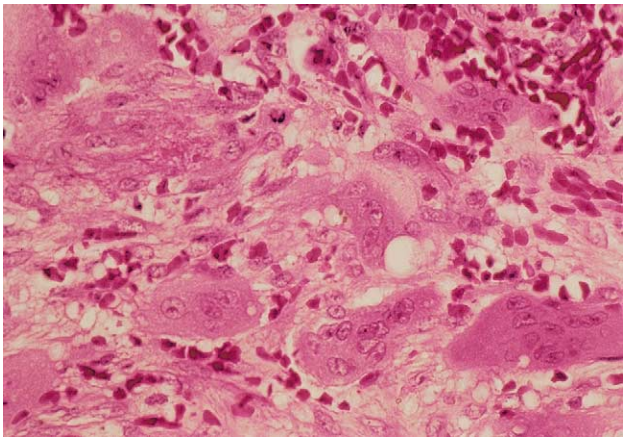

Figure 6. High-power view of the tumor displays spindle-shaped cells intermixed with many multinucleated giant cells, some of which contain 8 to 10 irregular nuclei and prominent nucleoli (stain, hematoxylin–eosin; original magnification, ×128).

Computed tomography (coronal and axial views) revealed bilateral, large, expansile bony lesions involving the lateral aspects of the orbital floors extending to the orbital apices, causing marked proptosis and superior displacement of the orbital contents (Figs 2, 3). The lesions constricted the orbital apices and displaced the lateral recti muscles to the orbital roof bilaterally. The left orbital lesion extended into the posterior wall of the maxillary sinus. Similar lesions were found in the maxillae, edentulous mandible, hard palate, and pterygoid plates. A complete hematologic workup, including alkaline phosphatase, serum calcium, and phosphorus, was normal.

The patient had a clinical diagnosis of cherubism at age 4 years, and as a result of difficulties with speech and eating, she underwent three maxillary and mandibular osteoplasties between the ages of 18 and 24 years. Aside from the proband, there are four children in the family: an unaffected brother 6 years older; a sister 5 years older with mild radiographic changes but no clinical manifestations of the disease; a brother 1 year older who had mild maxillary but massive mandibular lesions, all of which spontaneously and completely regressed after puberty; and a sister 2 years younger who underwent mandibular sculpting at age 9 with exuberant recurrence of the lesion followed by spontaneous regression at puberty. The parents show no clinical evidence of cherubism (radiographic imaging was declined).

Because of signs of early right optic nerve dysfunction and intractable diplopia, the patient underwent surgical excision of the orbital lesions through a bicoronal incision. The lesions were debulked with bone curettes and rongeurs without adverse bleeding. Residual lesions remained in the left pterygopalatine fissure, and a thin cortex of bone was preserved to compartmentalize the temporal lobe. Large reddish brown, friable, vascular masses surrounded by calcified cortex were excised.

Histopathologic evaluation of the orbital lesions revealed a stroma composed mostly of spindle-shaped fibroblasts intermixed with scattered multinucleated giant cells of variable size (Figs 4–6). Numerous small vascular channels and reactive bone were also observed.

Eighteen months postoperatively, the optic nerve dysfunction, proptosis, and diplopia in upgaze remained. Her vision returned to 20/20 in each eye, and her visual field defects resolved. Seven years after her initial orbital surgery, she had a recurrence in the left orbital floor with direct compression on the midorbital portion of the optic nerve that caused a sudden decrease in vision from both a branch retinal vein occlusion and compressive optic neuropathy. She underwent transorbital debulking with successful resolution and recovery to 20/20 vision.

Discussion

Cherubism is a rare inherited disorder that involves the facial bones. Typically, patients develop facial fullness because of enlargement of the bones occurring between the ages of 2 and 4 years, associated with abnormal dentition or submandibular lymphadenopathy. In the most benign cases, only the angles of the mandible are affected; however, the lesions might spread to involve the entire mandible with the exception of the condyles. In more severe cases, the maxilla is also involved, usually beginning in the tuberosity and extending to the antral floor or even the anterior wall.[8] The development of inferior scleral show, which gives these patients their characteristic cherubic appearance, is due to either a lower lid retraction in relation to the diffuse enlargement of the lower half of the face or to an upward displacement of the eye from a mass involving the orbital floor.[4] Usually the disease progresses until puberty, when the lesions demonstrate arrest and often regression, leading to a normal adult appearance in most patients. Radiologically, the lesions appear as multiloculated cysts with thinning of the overlying cortex, but as they enlarge, the cysts display a ground-glass appearance and eventually might regress and evolve into normal-appearing bone.[9]

Proptosis and decreased visual acuity caused by optic nerve impairment are other ophthalmic manifestations that have been described.[4,8] In the case reported herein, the main ocular findings were incyclotorsion with diplopia and compressive optic neuropathy. The orbital lesions caused a profound rotational displacement of the globes and extraocular muscles such that the primary vectors of extraocular muscle actions were misdirected. There was no paralytic or restrictive component to the strabismus. This type of motility imbalance is uncommon and has not been well documented in cherubism.

Another unique clinical feature in this case is the onset of orbital symptoms. Typically, the condition is manifested in the first 5 years of life, and the lesions grow until the age of 7. In the late teens, the mandibular lesions often show regression, whereas those involving the maxilla are less likely to spontaneously resolve.[10] In the case reported herein, the ocular symptoms developed in the third decade of life, whereas the lesions of the mandible and maxilla remained stable. Furthermore, the bilateral orbital lesions were slowly progressive over a period of almost 2 years, causing diplopia and early optic nerve impairment. The late age of onset and relatively slow progression of the orbital lesions suggest a variation of the usual pathologic process.

The histopathologic features of the orbital tumors are those of a GCRG. There are several orbital lesions with prominent multinucleated giant cells. These entities include the brown tumor of hyperparathyroidism, aneurysmal bone cyst, giant cell tumor of bone, and GCRG.[11] In this case, the levels of calcium and phosphorous were normal, thus excluding hyperparathyroidism. The lack of cystic appearance or fluid levels on computed tomography scan and absence of large irregular blood-filled spaces by light microscopy are inconsistent with a diagnosis of aneurysmal bone cyst.[12]

The differential diagnosis between GCRG and giant cell tumor of bone might be difficult. Both might destroy bone and macroscopically appear as reddish-blue, friable vascular tissue. However, the giant cells of GCRG usually are arranged in clusters around foci of hemorrhage in contrast to the giant cell tumor of bone in which the giant cells dominate the entire field, are larger, and contain numerous plumper nuclei that are identical to those of the stromal cells. In addition, in GCRG, the stroma usually shows spindle-shaped fibroblastic cells, areas showing collagen deposition, and foci of bone formation. In giant cell tumor of bone, the latter finding is usually absent.

There are also clinical differences between giant cell tumors of bone and GCRG. Most giant cell reparative granulomas occur in patients between 10 and 25 years of age, a history of trauma is sometimes elicited, and these lesions are usually self-limited, might resolve spontaneously, and recur in only 10% to 15% of cases.[12] In contrast,

giant cell tumors of bone occur more commonly in females between 20 and 40 years of age, have a predilection for the lower femur and upper tibia in 70% to 75% of the cases, and rarely involve the craniofacial regions. Some authors believe that giant cell tumor of bone does not involve the jawbones except in patients with Paget's disease.[12]

The diagnosis of bilateral GCRG in our patient with cherubism is strongly supported by the histopathologic features of the orbital lesions coupled with the clinical manifestations, age of onset, rate of growth of the lesions, and severity of the orbital symptoms. Both clinicians and pathologists involved in the diagnosis and treatment of orbital lesions should be aware of the preceding findings and consider the diagnosis of GCRG occurring in patients with the clinical manifestations of cherubism.

References

1. Riefkohl R, Georgiade GS, Georgiade NG. Cherubism. Ann Plast Surg 1985;14:85–90.
2. Jones WA. Familial multilocular cystic disease of the jaw. Am J Cancer 1933;17:946–50.
3. Chomette G, Auriol M, Guilbert F, et al. Cherubism: Histoenzymological and ultra structural study. Int J Oral Maxillofac Surg 1988;17:219–23.
4. Hawes MJ. Cherubism and its orbital manifestations. Ophthal Plast Reconstr Surg 1989;5:133–40.
5. Colombo F, Cursiefen C, Neukam FW, et al. Orbital involvement in cherubism. Ophthalmology 2001;108:1884–8.
6. Carroll AL, Sullivan TJ. Orbital involvement in cherubism. Clin Experiment Ophthalmol 2001;29:38–40.
7. Ueki Y, Tiziani V, Santanna C, et al. Mutations in the gene encoding c-Abl-binding protein SH3BP2 cause cherubism. Nat Genet 2001;28:125–6.
8. Marck PA, Kudryk WH. Cherubism. J Otolaryngol 1992;21: 84–7.
9. Som PM, Lawson W, Cohen BA. Giant-cell lesions of the facial bones. Radiology 1983;147:129–34.
10. Peters WJ. Cherubism: a study of twenty cases from one family. Oral Surg Oral Med Oral Pathol 1979;47:307–11.
11. Hoopes PC, Anderson RL, Blodi FC. Giant cell (reparative) granuloma of the orbit. Ophthalmology 1981;88:1361–6.
12. Unni KK. Dahlin's Bone Tumors: General Aspects and Data on 11,087 Cases. 5th ed. Philadelphia: Lippincott-Raven; 1996.