

Case Report

Locally aggressive orbital giant cell reparative granuloma in an infant: case report and literature review

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Received September 16, 2020; Accepted November 16, 2020; Epub June 15, 2021; Published June 30, 2021

Abstract: Giant cell reparative granuloma (GCRG) is a non-neoplastic hyperplasia of bones that mostly happens in the mandible and maxilla in any age group but has a predilection for children and young adults. GCRGs that cause bone destruction are of very low frequency. Orbital-involved cases have been rarely reported since 1981, especially in children. We now report a 1-year-old girl with a rapidly enlarging post-traumatic orbital mass. CT scan and surgical resection showed a well-defined mass occupying the upper right orbit, causing bone destruction. Microscopically there was a proliferation of histocytes and some osteoclast-like multinucleated giant cells with hemosiderin, finally confirmed to be GCRG. 22 months' follow up showed no evidence of recurrence. This case suggests infant orbital GCRG can be locally aggressive.

Keywords: Orbit tumor, histopathology, trauma, giant cell reparative granuloma, infant

Introduction

Giant cell reparative granuloma (GCRG) is a non-neoplastic reactive tumor of bones, earliest mentioned by Jaffe in 1953 [1]. The etiology remains unclear though trauma and chronic inflammation are considered potential triggers. The lesion seems to happen in any part of the body with a predilection for mandible and maxilla. Apart from those involved inferiorly by an enlarged mandible in cherubism [2, 3], orbital onset was rarely reported since 1981 [4-13]. Most GCRGs are solitary, while multifocal lesions were reported to be in fingers, maxilla, or mandible [14]. No sarcomatous transformation or aggressive spread of the lesion has been noted. GCRGs are a tumor-like lesion of benign nature, and mostly tend to be localized and grow slowly but a few locally aggressive cases causing bone destruction were reported [15-17]. GCRGs mostly occur in children and young adults, and females are more often affected [14]. It is rare to report a 1-year-old infant with orbital GCRG that was treated surgically without any adjuvant therapy and had a long-term good prognosis.

Case report

A 1-year-old infant came to our clinic with ptosis of the right eye with no obvious pain or redness. She had crashed onto a door frame on the upper right orbit 1 month before. A palpable mass was noticed on the spot. As time went on, it showed no tendency to disappear. No significant medical history or family history of other diseases was noted.

Physical examination disclosed slight swelling and ptosis of the right eye. A palpable mass with a smooth surface was located on the outer superior orbital margin, which was well-circumscribed and moderately textured, showing poor activity and no tenderness (**Figure 1**). No notable influence in eye movement and visual acuity was seen. There was no abnormal finding of systemic, serum or biochemical examination.

CT scan revealed a high-density soft tissue mass with mildly enhanced scanning in the upper right orbit, interrupting bony continuity and stretching into the orbital cavity, causing eyeball dislocation. The transversal surface of the lesion measured 3.2 cm×1.9 cm, and the

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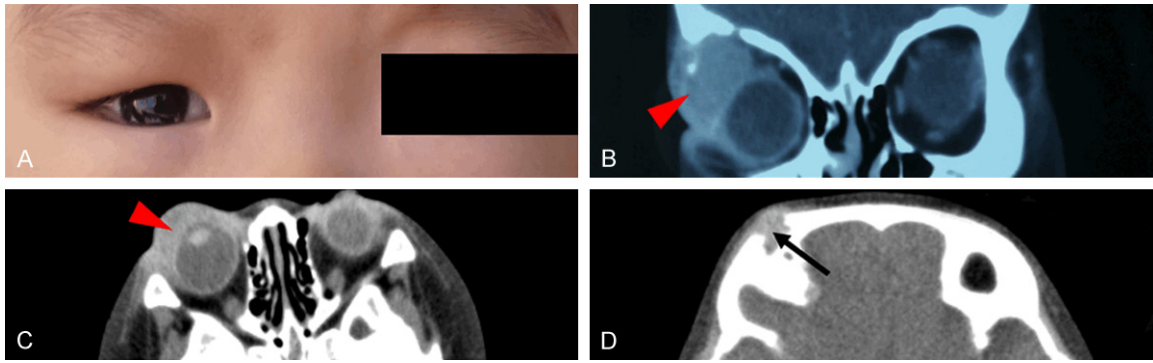


Figure 1. Clinical photograph at presentation showing a right orbital mass with ptosis (A); Coronal (B) and horizontal (C and D) CT scan demonstrate that the mass extended into the right orbit, causing bone destruction (black arrowhead) and blurred border of eyeball (red arrowheads).

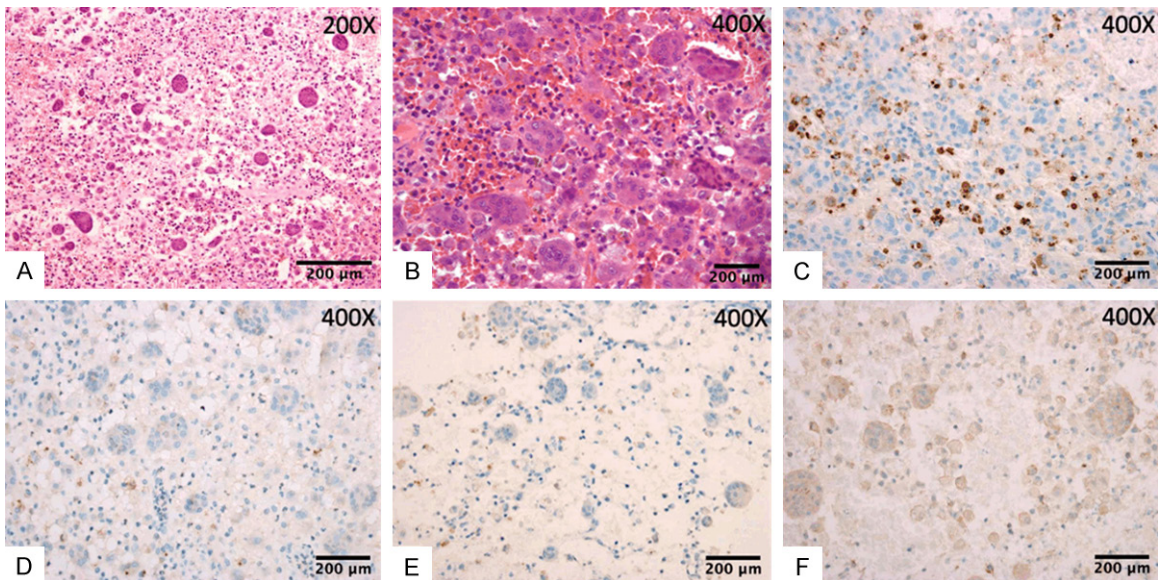


Figure 2. A. Photomicrograph of the mass section showing histocyte proliferation (hematoxylin-eosin, original magnification, $\times 200$). B. Numerous osteoclast-like multinucleated giant cell scattered in fresh hemorrhagic background, some of which contain hemosiderin (hematoxylin-eosin, original magnification, $\times 400$). C. S-100 staining of some cells revealing cytoplasmic immunoreactivity (S-100, original magnification, $\times 400$). D. CD1a staining of cells showing no immunoreactivity (CD1a, original magnification, $\times 400$). E. Langerin staining of cells showing no immunoreactivity (Langerin, original magnification, $\times 400$). F. P63 staining of cells were negative (P63, original magnification, $\times 400$). Scar bar = 200 μm .

boundary between the mass and anterior wall of the eyeball was blurred (**Figure 1**). Enlargement of right parotid lymph nodes was noted (1.0 cm \times 1.0 cm). No underlying bone diseases were observed.

During the surgical excision and additional curettage, the mass was removed from subperiosteal space of the upper right orbit. The involved orbital periosteum was thick and intact with uneven surface. Gross specimen sh-

owed a pile of red brown and crispy tissue measuring 1.8 cm \times 1.5 cm \times 0.2 cm. H&E staining revealed histocyte proliferation and some osteoclast-like multinucleated giant cells with hemosiderin. Immunohistochemistry was positive for S-100 protein staining, while CD1a, langerin, and P63 staining were negative (**Figure 2**). Thus, the pathologic diagnosis of orbital giant cell reparative granuloma was confirmed. 22 months of follow up revealed no evidence of clinical recurrence.

Discussion and conclusion

Giant cell reparative granuloma (GCRG) is also called Giant Cell Granuloma (GCGs). There are two subtypes of GCRGs: central and peripheral ones. The former is bone-based while the latter is soft tissue-related. Central Giant Cell Granuloma (GCGCs) usually occurs in maxilla, mandible, and cranial bones while Peripheral Giant Cell Granuloma (PGCG) is most observed to affect mucosa in the oral cavity [18]. Both of them share the same histologic characteristics with each other [15]. As etiology remains unknown, the word “reparative” for giant cell reparative granuloma (GCRG) marks the reaction to intraosseous hemorrhage by Jaffe [1], which may be secondary to trauma or chronic inflammation. In this case, a history of blunt trauma was noted. Primary cholesteatoma has a relevance to GCRG onset [19]. Another possible inducement is hormone stimulation, because GCRGs affect females more frequently than males, and more than one case with rapid growth of lesion during pregnancy or the postpartum period were reported [14, 20]. Just a few orbital GCRGs cases have been reported since 1981, fewer in pediatric patients. To our knowledge, the youngest orbital-involved patient was 3-months old, and was treated with Zoledronic acid after surgery and had no recurrence in 2 years of follow-up [5]. However, the research lacked further more detailed information about orbital case, such as past history, or radiologic findings. Medication intervention was performed following surgical treatment, unlike our case. Considering the unpredictable long-term side effects of drugs like Zoledronic acid on an infant, medication was not applied in our case. In addition, there were also spontaneous bone healing cases reported in pediatric patients [21, 22], so we treated this 1-year-old infant surgically without any other adjuvant therapy. After 22 months’ follow-up, the girl showed no recurrence of the lesion.

For most GCRGs, painless deformation of involved bones or soft tissues may cause functional disturbance or displacement of adjacent tissue [18]. Neurologic dysfunction also happened in some certain situations [19]. GCRGs tend to be silent and relatively stable. A few cases showed local aggressiveness with rapidly developing painful masses [15], but they rarely had wide-ranging bone destruction that

required long-term multidisciplinary intervention [22]. In our case, clinical symptoms showed a painless mass that caused slight eyeball displacement without facial paralysis or disfigurement. Bone destruction with an uneven surface that quickly formed within a month showed the aggressive behavior of the lesion. In addition, enlargement of lymph nodes is not a common sign of GCRGs, but it might be a hint of previous infection.

Orbital mass lesions can be related to inflammation, infection, hemorrhage, neoplasm, metastasis, and development [23]. To identify GCRGs, the propensities of race, gender, age, location, and detailed history should be taken into consideration. The atypical clinical manifestations and radiological findings have limited diagnostic value to distinguish malignant and benign tumors [23], especially for GCRGs which are of benign nature but may act malignantly. Thus, histopathology still is the gold standard for differential diagnosis.

Uniform cellular stroma with fibroblastic or fibro-histiocytic background with oval to spindle shaped and mononuclear infiltrative cells, and multinucleated giant cells scattered around intraosseous hemorrhage foci are included in the histologic features of GCRGs; sometimes reactive osteoid formation or hypervascularity are also present [4, 14, 15, 24]. S-100 proteins play important roles in regulating immune homeostasis, post-traumatic injury, and inflammation [25], which was stained positively in this case, showing the evidence of reparative process secondary to the intraosseous hemorrhage. Langerin protein, which is expressed on Langerhans cells, plays a role in healing the wounds. Depletion of langerin (+) cells enhances cutaneous wound healing which may account for the negative staining for langerin in this case [26]. P63 is related to proliferation, differentiation, DNA damage response, and metabolism, and may be involved in some tumor progression [27]. Absence of p63 expression is typical of most soft tissue tumors, and that matches findings in this case [28]. CD1a staining is frequently used to identify the presence of an abnormal proliferation of Langerhans cells and contributes to the diagnosis of Langerhans cell histiocytosis [29]. It has potential anti-mycobacterial immunity as well [30]. Thus, the negative staining for langerin, P63,

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and CD1a are useful for differential diagnosis of GCRG.

The differential diagnosis of GCRGs is extensive. Giant cell tumor of bone shares high similarity with GCRGs featuring proliferation of mononuclear stromal cells and numerous but larger osteoclast-like giant cells that contain more nuclei, and more diffusely distributed than GCRGs [4]. Besides, predilection of anatomic location, absence of traumatic history, and underlying bone disease are secondary differential points for GCTs [31]. Cholesterol granuloma is quite similar to orbital GCRGs for frequent involvement of the supra-temporal quadrant of orbit with or without certain traumatic history, causing local bone erosion [32]. However, a yellow cheesy-like content in the gross specimen and microscopic evidence of cholesterol clefts or absence of epithelial elements are distinctive features [32-34]. Langerhans cell histiocytosis is a multi- or unisystematic, multifocal or solitary lesion that involves bone and adjacent soft tissue. When it occurs in the orbit, atypical clinical and radiologic findings are indistinct and histopathology is diagnostically necessary. The typical characteristics include numerous histiocytes with giant cell formation and scattered eosinophilic granulocytes. CD1a and S-100 positive staining confirm Langerhans cells presence [35]. Aneurysmal bone cyst is a bone cyst composed of large vascular spaces full of blood. In GCRGs there are smaller blood-filled spaces and cystic sinuses and a majority of a solid component [36]. Brown's tumor of hyperparathyroidism is hard to tell from GCRG histologically, but it can be easily excluded by laboratory testing of parathormone, blood calcium, and phosphorus [6].

In summary, we presented a rare case of post-traumatic orbital GCRG in a 1-year-old infant with bone destruction. Treated surgically, the patient showed no recurrence at 22 months of follow-up. Pediatric orbital GCRG at age of 1 year old or younger is rarely reported. Trauma is a risk factor for GCRG. A diagnostic dilemma was encountered since there were atypical clinical and radiologic features that overlap with other bone tumor-like lesions. Thus pathologic examination is necessary for definite diagnosis. Although GCRG is not a malignant lesion, the risk of sarcomatous transformation should be avoided by surgery [6]. Radical curettage

and excision are the most effective treatments for GCRG and can reduce its recurrence. There are many other treatments proven to be ineffective, such as intralesional corticoid injections, calcitonin therapy, radiotherapy, and pharmacologic anti-inflammatory treatment. Further research is still on the way. In addition, long-term follow-up is essential to assess the prognosis of GCRG.

Acknowledgements

The authors are grateful to the patient and her family for signing informed consent for publication. This study was supported by a grant from the 1.3.5 Project for disciplines of excellence-Clinical Research incubation Project, West China Hospital, Sichuan University (2018HXF-H024) and Sichuan provincial science and technology program (18ZDYF1977). This study complied with the tenets of the Declaration of Helsinki. IRB approval was exempted because this was only case report.

Disclosure of conflict of interest

None.

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