

Orbital Giant Cell Tumour in a Paediatric Age Group

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Abstract: *Giant cell tumour (GCT) of the bone is generally a benign but locally aggressive tumour that is primarily composed of multinucleated osteoclast-like giant cells with a background of neoplastic mononuclear stromal cells. It predominantly occurs in the epiphysis and metaphysis of the long bones but it can occur in an unusual locations. Giant cell tumour of the skull is rare and GCT of the orbital bones account for less than 1% of all GCTs. Accurate histopathological diagnosis of GCT and differentiating GCT from other pathological mimickers are important as the GCT has a tendency for local recurrence in incompletely resected cases and in the view of the recently emerging targeted therapy for GCT. Herein we present a case of orbital GCT, which occurred in the left orbital roof in a 6-year-old girl. The tumour was surgically resected and the patient remained with no evidence of residual or recurrent disease after 42 months postoperative follow-up period. In addition, we review the histopathological mimickers of GCT with an emphasis on the pathological diagnostic pitfalls.*

Keywords: Giant cell tumour; GCT; orbit; orbital roof; paediatric

1. Introduction

Giant cell tumor (GCT) of the bone is a benign but locally aggressive and destructive tumor and has a high tendency for local recurrence. Histologically, GCT is composed of primitive round to spindle, mononuclear, collagen-producing neoplastic cells and evenly distributed giant cells with osteoclastic activity [1]. Primarily, GCTs affect adults between 20-40 years of age [2]. The vast majorities of the GCTs affect the epiphysis and the adjacent metaphysis of the long bones, most commonly the distal femur and proximal tibia, but may occur in the distal radius, sacrum, vertebral body, fibular head, proximal femur, proximal humerus, small bones of the hands and

feet and pelvis [2-4]. Less than 2% of all GCTs affect the skull and GCTs involving the orbital bones are exceedingly rare [5]. Rarely, GCTs can affect the immature skeleton of the children and adolescences and in such cases they tend to be located primarily in the metaphysis in contrast to the predominantly epiphyseal localization in adults [2, 6, 7]. Accurate radiological and pathological diagnoses of the GCT of the bone are important for proper surgical and therapeutic decisions and follow up planning. Herein, we report the clinical and the pathological findings of a rare case of a left orbital roof GCT in a child who was surgically treated, and briefly review the morphological mimickers and the histopathological diagnostic pitfalls.

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2. Case Report

A 6-year-old, healthy girl presented with a slowly progressive left eye swelling over 2 years period and mild eyeball pain. There was no history of recent or remote history of ocular or periorbital trauma. On physical examination, left eye proptosis was evident as well as mild orbital tenderness on palpation. The extraocular movements were full and the patient's visual acuity was not affected.

An axial contrast computed tomography (CT) scan and magnetic resonance imaging (MRI) (Figure 1A and 1B) showed an intraorbital, intraosseous, lobulated, expansile, hyperdense and homogenous lesion in the left orbital roof, measuring 2.3 x 2.2 x 2.9 cm. The lesion was primarily involving the frontal bone, exerting a mass effect inferiorly on the eyeball as well as superiorly over the anterior cranial fossa, and expanding the cortex that appeared thinned out but there was no periosteal reaction. No internal calcified matrix or intralesional haemorrhage was seen within the lesion. The intraocular muscles as well as the retrobulbar fat were within normal limits. The contralateral orbit was unremarkable. The brain and the posterior fossa structures revealed no abnormalities. The radiological differential diagnosis was wide and included intraosseous meningioma, schwannoma, dermoid cyst, eosinophilic granuloma and sarcomas.

The patient underwent surgical resection of the lesion. An intraoperative consultation and frozen section examination revealed a giant cell-rich cellular lesion. The lesion was resected with an attempt of complete removal of lesional tissue. Grossly the resected lesion was received as multiple, irregularly-shaped fragments of soft to firm, brown and haemorrhagic tissue that measured 7.5 x 4.0 x 2.0 cm in aggregate.

Sections from the specimen were fixed in 10% buffered formalin, paraffin-embedded, sectioned at 5 µm, mounted on coated glass-slides and stained by routine haematoxylin and eosin stain. A panel of diagnostic immunohistochemical (IHC) stains was performed. All immunoassays were performed according to the manufacturer's guidelines, using an automated platform (Ventana Benchmark XT, Tucson, AZ, USA), and heat antigen retrieval by ultracell condition solution PH 8.4. An ultra view universal DAB detection kit was used for reaction visualisation. Proper positive and negative controls were utilised for all special and IHC stains.

Histopathological examination showed GCT of the bone. The tumour was cellular and consisted of neoplastic round to spindle-shaped mononuclear stromal cells and numerous, variably-sized, osteoclast-like multinucleated giant cells distributed throughout the tumour (Figure 1A). The mononuclear neoplastic cells had round to oval, normochromic to slightly vesicular nuclei, indistinct nucleoli, small volume of pale amphophilic cytoplasm and poorly-defined cell membranes. Rare mitotic figures were seen in the mononuclear neoplastic cells but no atypical mitoses were noted. Scattered foam cells (Figure 1B), lymphocytes (Figure 1C) and rare eosinophils were seen

admixed with the neoplastic cells. No nuclear pleomorphism was seen and there was no evidence of malignant osteoid formation. Focal haemorrhage was noted but there was no cystic degeneration and or tumour necrosis. Areas of which the tumour was eroding into the surrounding resected orbital bone were seen. The extent of the tumour resection could not be evaluated due to the fragmented nature of the specimen.

Immunohistochemically, the single and multinucleated cells were positive for CD68, while staining for p63 was negative and immunostaining for Ki-67 proliferating index demonstrated nuclear positivity in approximately 20-25% of the mononuclear neoplastic cells.

The post-operative clinical course was uneventful. No adjuvant therapy was implemented. Periodic clinical and radiological follow up showed no evidence of residual tumour or recurrence of the disease 42 months after surgery.

3. Discussion

Giant cell tumour of the bone is a benign, predominantly unifocal, locally aggressive and destructive tumour, with a relatively high-recurrence rate. It counts for approximately 5% of all primary bone tumours and mainly affects adults between the ages of 20 and 40 years with a slight female preponderance [2, 8]. Approximately 90% of the GCTs involve the epiphysis of long bones and less than 2% involve the skull and occur most frequently in the sphenoid and temporal bones; in very rare instances, GCTs can involve the orbital bones [5, 9, 10]. Approximately 16% of the GCTs occur in patients less than 20 years of age [8], and only 0.8-7.5% of all GCTs occur in pediatric patients, who are skeletally immature [11]. Orbital bone GCTs in pediatric age group are extremely rare and only 3 orbitofrontal GCTs were previously reported in children [5, 12, 13]. Those patients were two 10-year-old males [12, 13] and a 2-year-old female [5], who all had complete resection of the tumour. Similar to our patient who showed no clinical or radiological evidence of recurrence 42 months after surgical resection, there was no tumour recurrence in 1 of the male patients after 4 months follow-up period [13], while the female patient reported by Kamoshima et al [5], had a recurrent disease after two incomplete surgical removal of the tumour.

Clinically, orbital GCTs present as an enlarging mass, eye soreness and tenderness, proptosis, diplopia and oedema of the eyelid. Giant cell tumour of the bone is an expansile, lytic, osteoclastogenic tumour that radiologically appears as a radiolucent, well-defined, hyperdense contrast enhancing lesion [14, 15]. However, not all radiological studies can sufficiently delineate these characteristic features of GCT to allow a proper preoperative diagnosis particularly in rare locations such as the orbit [9, 12]. In our patient the radiological differential diagnosis included a variety of benign and malignant bone lesions and GCT was not among them.

The histopathogenesis of GCT is not yet fully understood and it remains a matter of controversy. Histologically,

GCT is characterised by numerous, uniformly distributed, multinucleated osteoclast-like giant cells, admixed with proliferating bland, spindle- and oval-shaped neoplastic stromal cells and variable numbers of lymphohistiocytic inflammatory cells [1, 16]. Accurate radiological and pathological diagnosis of GCT from other bone lesion, particularly from giant cell forming bone lesions can be challenging and is important for the following reasons: (1) despite the bland morphological appearances of the GCT, it is locally an aggressive and destructive tumour with an unpredictable biological outcome and tendency of high rate of local recurrence that reaches up to 40-50% after curettage that usually leaves microscopic disease; hence the recommended therapeutic approach is complete surgical removal with local adjuvant therapies [2, 17], (2) approximately 3-5% of patients with GCT develop pulmonary metastasis, of which the metastatic tumour appears histologically identical to the primary GCT and may be associated with poor unfavorable outcome [18, 19], (3) rarely GCTs can spontaneously or post adjuvant radiotherapy dedifferentiate and transform into a histologically overt malignant tumour, mainly high-grade osteosarcoma and associated with very poor clinical outcome [20] (4) and lastly, the emerging role of denosumab, which is a receptor activator of nuclear factor κ B ligand (RANKL) inhibitor overexpressed by the mononuclear neoplastic cell and promotes the recruitment of the multinucleated giant cells in the tumour and their bone resorption; thus exerts a biological effect that stabilize the local and metastatic disease [14, 16]. All these facts warrant an accurate preoperative diagnosis, which has a great impact on the surgical management, post adjuvant therapy and follow-up planning.

The histopathological differential diagnosis of orbital GCT includes various giant cell-containing, benign and malignant lesions and tumours. One of the most challenging histopathological differential diagnoses is giant cell reparative granuloma (Brown tumour of hyperparathyroidism), which is a benign, reactive, intraosseous lytic, often multifocal lesion occurring in the setting of hyperparathyroidism. Although it can histologically resemble GCT of the bone, the numerous giant cells in giant cell granuloma tend to be in a background of vascularised, fibrotic stroma, have fewer numbers of nuclei and aggregated around a haemorrhagic area [21]. Non-ossifying fibroma (fibroxanthoma) is a common non-neoplastic bone lesion, which occurs in the metaphysis of the paediatric patients and histologically characterised by the presence of proliferating spindle-shaped, bland fibroblasts that arranged in short fascicles and storiform pattern, fibrotic stroma and minor component of scattered osteoclast-type multinucleated giant cells [22]. Another important histological differential diagnosis is primary aneurysmal bone cyst, which is a benign, osteolytic and expansile bone lesion, typically involves the long bones but may rarely arise in the orbit, most commonly in the orbital roof [23, 24]. It is characterised by forming variably-sized, blood-filled spaces that are separated by variable amount of fibrotic stroma. These spaces are devoid of endothelial lining and the intervening stroma consists of loose spindle fibroblasts and contains histiocytes, haemosiderin, reactive woven

bone and clusters of unevenly distributed osteoclast-like multinucleated giant cells, often around the blood-filled spaces. Giant cell-rich osteosarcoma is an uncommon, high-grade variant of osteosarcoma that exceedingly rare to occur in the head and neck region and is characterised by the presence of numerous, uniformly distributed osteoclast-like giant cells amidst spindle or oval mononuclear and undifferentiated neoplastic cells embedded in fibrovascular stroma and associated with the malignant osteoid formation [25, 26].

4. Conclusion

In summary, we reported the clinical, radiological and histopathological characteristics of a very rare case of orbital GCT in paediatric age group patient. Despite its very rare occurrence in the orbital bone, GCT should always be in the radiological and pathological differential diagnosis of reactive as well as benign and malignant bone lesions. Recognising GCT from other histopathological mimickers and establishing an accurate diagnosis are essential for proper treatment and follow-up planning.

Conflict of Interest:

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Conflict of interest: None

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Legends

Figure 1: Magnetic resonance images demonstrating (A) expansile, hyperdense and homogenous lesion in the left orbital roof, involving the frontal bone, (B) left eye proptosis.

Figure 2: Histopathological examination of giant cell tumour of the orbital roof: (A) the tumour consisted of oval-round and spindle-shaped mononuclear neoplastic cells and uniformly distributed, osteoclast-like multinucleated giant cells, (B) foam cells [arrows] and (C) mononuclear inflammatory cells [arrows] admixed with the mononuclear neoplastic cells were present (A – C Haematoxylin and Eosin stain x200).

Images

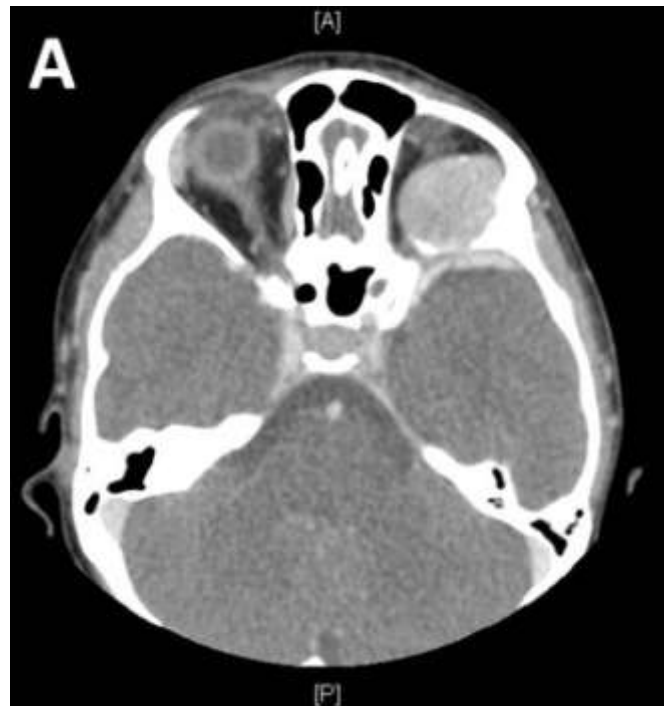


Figure 1A

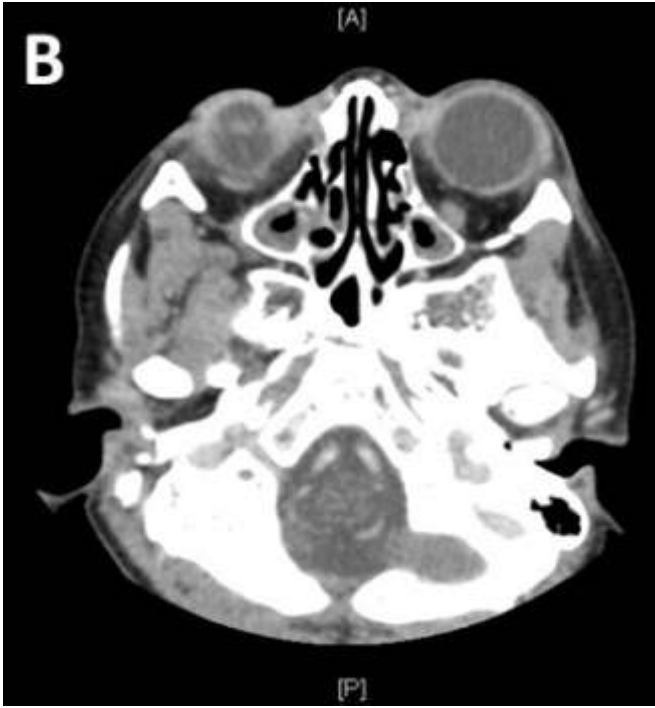


Figure 1B

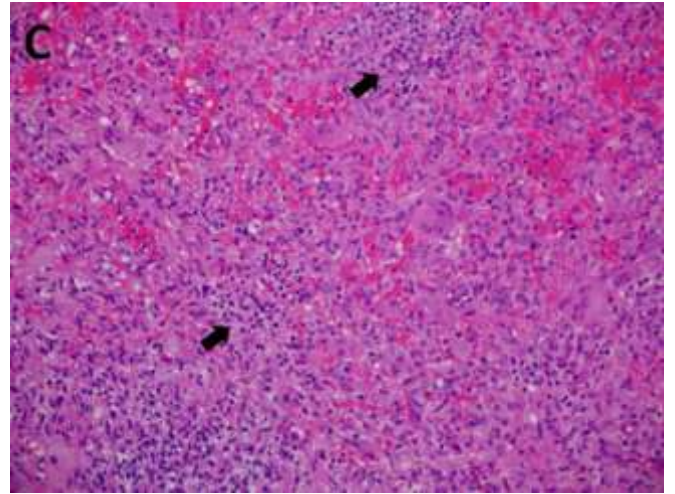


Figure 2C

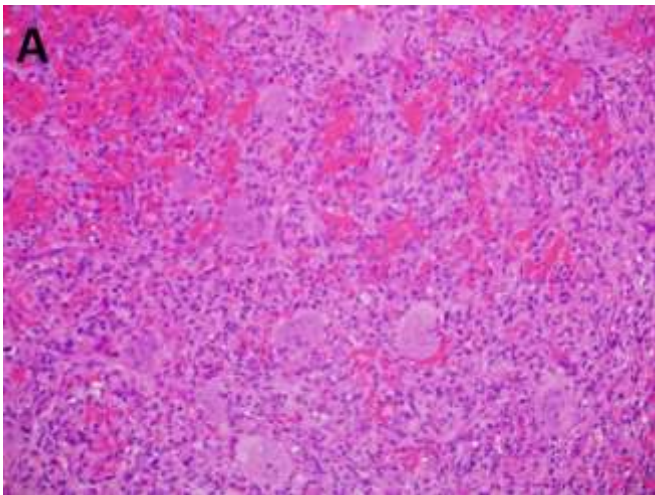


Figure 2A

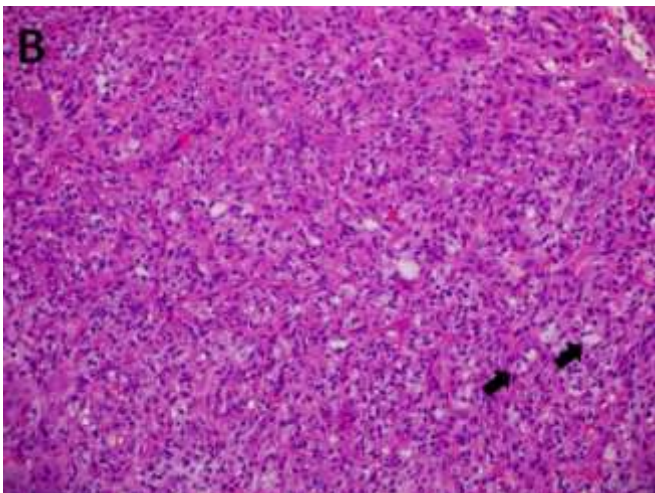


Figure 2B