Pathol. Oncol. Res. (2009) 15:291–295
DOI 10.1007/s12253-008-9124-y

ORIGINAL PAPER

Giant Cell Tumour and Central Giant Cell Reparative Granuloma of the Skull: do These Represent Ends of a Spectrum? A Case Report and Literature Review

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Received: 7 July 2008 / Accepted: 5 November 2008 / Published online: 15 November 2008

Abstract Giant cell tumour (GCT) of bone is an uncommon primary bone neoplasm typically occurring at the epiphyses of long bones in young adults. They are osteolytic neoplasms with approximate local recurrence rates of 25%, and 2% of patients develop pulmonary metastases. These tumours appear very rarely in the skull, with those few reported cases arising predominantly in the sphenoid and occasionally the temporal bones. They demonstrate benign histological features, but are locally aggressive and surgical excision is the treatment of choice. It is widely believed that giant cell tumours should be distinguished from other giant cell lesions, importantly central giant cell reparative granulomata (CGCG) which are thought to have a lower recurrence rate and for which no cases of malignant transformation or metastases have been reported. Investigators have noted that giant cell lesions in the skull bones may be unique and that GCT and CGCG may be part of a spectrum of a single disease process. We present a case of a giant cell tumour of the temporal bone which illustrates and re-emphasises this concept and review the literature on these lesions.

Keywords Giant cell tumour · Giant cell reparative granuloma · Histology · Skull bone

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Introduction

Giant cell tumours (GCT) are uncommon, primary bone neoplasms which typically develop at the epiphyses of long bones in patients in their second to fourth decades of life [1]. They are osteolytic neoplasms with potential for local recurrence in approximately 25% of cases while 2% may develop pulmonary metastases [1]. They occur very rarely in the bones of the skull, but have been reported in the sphenoid and temporal bones in small series and case reports. It is widely believed that giant cell tumours should be distinguished from other giant cell lesions, importantly central giant cell reparative granulomata (CGCG) which are thought to have a lower recurrence rate and for which no cases of malignant transformation or metastases have been reported; however both lesions may require post operative radiotherapy in order to achieve local control [2–4]. Investigators have noted that giant cell lesions in the skull bones may be unique and that GCT and CGCG may be part of a spectrum of a single disease process [5–7]. We report a case of GCT of the temporal bone which illustrates the

merging features of CGCG and GCT and review the literature on these lesions.

Case History

A 32 year old man presented with a 2 1/2 year history of progressive hearing loss with right-sided ear pain and pre-aural swelling. There was no history of previous trauma to the site. Serum biochemical and haematological tests were unremarkable. Computed tomography (CT) scan revealed an expansile mixed sclerotic and lytic lesion measuring 3.4×4.8×3.7 cm centered on the floor of the middle cranial fossa extending laterally into the glenoid fossa and anterior mastoid. There was also extension into the middle ear posteriorly with associated opacification of mastoid air cells by secretions (Fig. 1a). Magnetic resonance imaging (MRI) demonstrated the lesion to be of predominantly low T1w and T2w signal and to undergo heterogeneous gadolinium enhancement (Fig. 1b–d). The patient underwent an infra-temporal fossa subtotal resection of the mass. The patient had an uncomplicated post-operative course and at 2 months post discharge has some occlusion difficulties secondary to temporomandibular joint destruction, but is otherwise well. Adjuvant treatment is being considered.

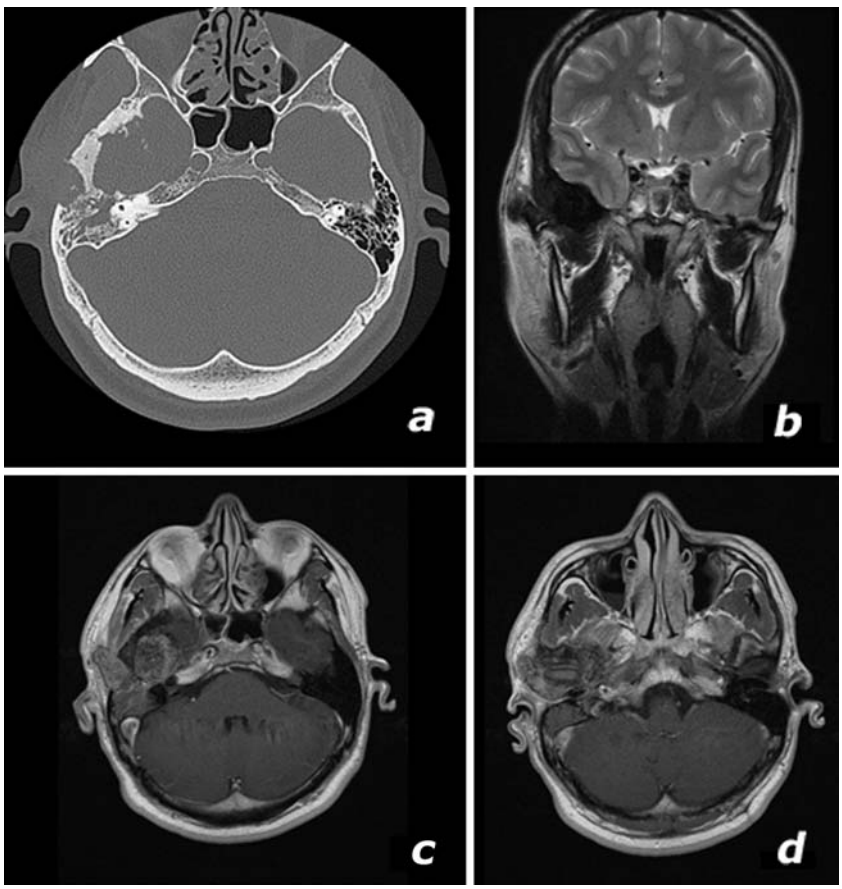

Fig. 1 Neuroradiology. Axial CT demonstrates a mixed lytic and sclerotic lesion of the right middle cranial fossa (**a**). Coronal T2-weighted (**b**) MRI scans show the lesion to be of low signal and axial post gadolinium T1-weighted images show it undergoes heterogeneous gadolinium enhancement (**c**, **d**)

Pathological Findings

Histology of the mass revealed a cellular lesion composed of sheets of uniformly distributed giant cells on a background of ovoid mononuclear cells with similar nuclei to those within the giant cells. Mitoses were inconspicuous and there were no atypical forms. There were foci of spindle cell areas with dense bands of fibro-collagenous tissue (Fig. 2a,c,d). There was infiltration of the soft tissue of the scalp while the adjacent bone showed sclerosis and marrow fibrosis (Fig. 2e). Perl's Prussian blue stain for ferric iron was strongly and extensively positive confirming abundant haemosiderin pigment due to old haemorrhages (Fig. 2b). Immunohistochemistry showed the Ki67 proliferation index to be approximately 5% (Fig. 2f). In our case there was no convincing immunolabelling with p63 and p53.

Discussion

The central giant cell reparative granuloma (CGCG) of the jaw bone was first defined by Jaffe in 1953 [8]. It has been described as a benign process limited to the mandible or maxilla and may be related to trauma and intraosseous haemorrhage, or infection and developmental abnormali-

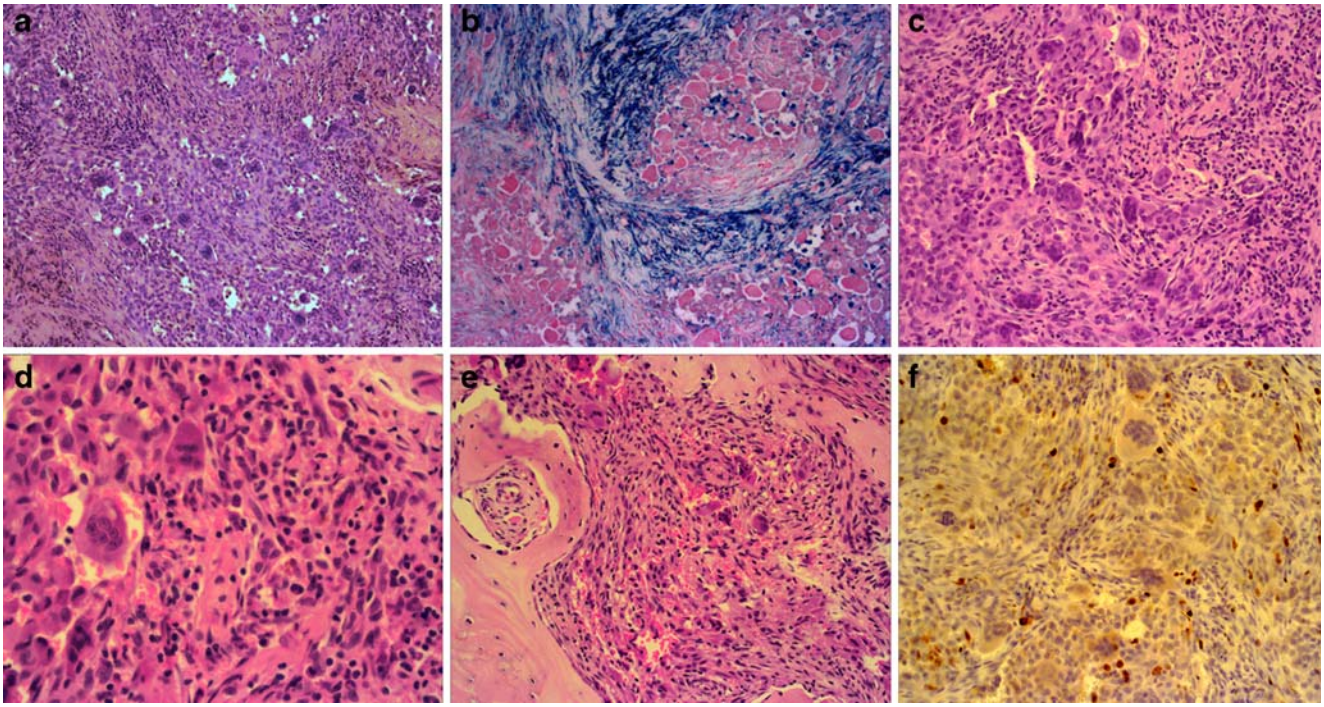

Fig. 2 Microscopic appearances. Histology sections reveal uniformly distributed giant cells (**a**, **c**) with interspersed sclerotic bands of collagen which contain abundant haemosiderin pigmentation (**b**). There are background mononuclear cells with nuclei similar to those within the giant cells and no cytological atypia (**d**). There is sclerosis of adjacent bone (**e**) and the Ki67 proliferation index is 5% (**f**). **a**, **c**, **d**, **e** Haematoxylin and eosin, **b** Perl's prussian blue, **f** Immunoperoxidase staining for Ki67. Original magnifications: 100× (**a**, **b**); 200× (**c**, **e**, **f**); 400× (**d**)

ties. The term was originally derived in order to distinguish these from giant cell epulis or peripheral giant cell reparative granulomas, which arise in the soft tissues of the jaw. They have since been reported to occur in the small bones of the hands and feet, orbit, paranasal sinuses, sphenoid and ethmoid [4].

Skull and facial bone giant cell lesions occur rarely, except within the mandible and maxilla. Bertoni et al [2] and Williams et al [4] have compiled the most recently published cases and there have been only a small number of additional case reports since [9–11]. Classical GCT of the bone occurs in patients over 20 years of age. They are more frequently seen in females than males. They usually arise at the epiphysis of long bones, most commonly the lower femur. Histologically GCTs are composed of stromal cells and giant cells. The giant cells have identical morphological and ultrastructural features to osteoclasts, and result from fusion of circulating recruited monocytes. It is well established that the stromal cell represents the only proliferating neoplastic component of the GCT. The stromal cells are mesenchymal in origin and ultrastructurally have features in common with fibroblasts or osteoblasts. They produce collagen Types I and III and have receptors for parathyroid hormone [12].

Radiographically, GCT is generally a purely lytic and expansile lesion with a thin cortical shell and possibly sclerosis or internal calcification. The MRI enhancement patterns may vary although they usually show a low intensity area on T2-weighted images due to associated haemosiderin and calcification [9]. The differential diagnosis on imaging includes CGCG, osteitis fibrosa cystica (brown tumour of hyperparathyroidism), osteolytic metastasis, plasmacytoma and chondroblastoma [13]. GCT and CGCG cannot be distinguished on imaging alone. Brown tumours can be excluded by normal serum calcium, phosphorus and alkaline phosphatase measurements. The metastases or plasmacytoma tend to show a more irregular pattern of bone destruction. Chondroblastoma shows a lobular architecture with chondroid differentiation and may have calcification in the centre.

There appear to be numerous overlapping features of GCT and CGCG arising in the skull bones. Hirschl and Katz [3] (Table 1) defined five major histological criteria in order to distinguish between the two lesions, but there are also borderline cases which show features of both. Indeed, in their 1974 paper, they reclassified 18 of 23 previously reported GCT into CGCG [3]. Both lesions appear more frequently in females however most patients with CGCG are less than 35 years old at the time of diagnosis [4] while 20–33% of patients with GCT are over 50 years of age [2]. Expression of p63 has been found by some to be useful to distinguish between GCT and other non-neoplastic giant

Table 1 Criteria for differentiation of giant cell reparative granuloma from giant cell tumour of bone—(modified from Hirschl and Katz [3])

	Giant cell reparative granuloma of bone	*Giant cell tumour of bone*
Age	<20 years old	20–40 years old
Location	Mandible; maxilla	Long bone epiphyses Skull (rare):sphenoid; temporal
Histological features	1. Giant cells in groups around haemorrhagic foci	1. Uniformly dispersed giant cells
	2. Stroma shows oval cells, many spindle shaped fibroblastic cells with zones of abundant collagen and relatively few giant cells	2. Stroma composed of plump, round and oval cells together with a rich vascular network
	3. Evidence of marked haemorrhage, with massive haemosiderin deposits in older lesions	3. Fresh haemorrhage is uncommon; haemosiderin deposits are rare and small
	4. Giant cells are smaller, irregular and elongated, with relatively few nuclei	4. Giant cells are larger, more rounded with many nuclei
	5. Foci of osteoid and new bone formation often seen in the middle of the lesion	5. Does not usually produce osteoid or new bone

cell lesions [14]. The term "giant cell lesion" was recommended for these equivocal cases [5].

Our case shared overlapping features of GCT and CGCG. The age and localisation was consistent with GCT. The histological appearances were equivocal with features predominantly of a GCT; i.e. uniformly dispersed giant cells, larger giant cells than in CGCG, no osteoid and new bone formation in the middle of the lesion, are in favour of a GCT. However, characteristics of a CGCG, such as marked haemorrhage with massive haemosiderin deposits and focally abundant collagen deposition were also present.

The importance of distinguishing between GCT and CGCG is based on the reported higher recurrence rates, risk of metastasis and malignant transformation of GCT. The recurrence rates of 25% are based predominantly on reports of GCT in long bones [1], not those occurring in the skull. It is well established that initial surgical removal is the most important factor in predicting the outcome of patients with GCT. Skull bone GCTs tend to occur in the sphenoid or temporal bones where extensive resection may not be practicable and morbidity and mortality has been related to incomplete elimination of the primary tumour [2]. Equally, others have reported recurrence rates as high as 69–75% for truncated removal of CGCG in the jaw [6]. There have been only two reported cases of metastasis from a GCT of the skull [5], one of which originated in a patient with Paget's disease [15]. It is of interest that nearly all cases of metastases of long bone GCTs have emerged after surgical manipulation to the primary tumour. No cases of metastatic CGCG have been documented. It may be that therapeutic recommendation to treat incompletely excised CGCG with adjuvant radiotherapy has minimized the risk of recurrence or metastasis.

There is no doubt that GCT of the skull may be locally aggressive and can be fatal. It has remained difficult to identify features of these lesions which may help to predict aggressive behaviour [6, 7]. This is not surprising as giant cell tumours of the long bones have also been notoriously enigmatic in their behaviour with radiographically and histologically benign appearing tumours resulting in metastases. Recent studies have even found that these tumours comprise a polyclonal population [16]. There are differing opinions on the ability of DNA ploidy analysis and proliferation index measurement to predict prognosis. Some researchers have found that aneuploid tumours [17, 18] with high proliferation indices are more likely to recur [19], while others have shown that DNA flow cytometry [20, 21] and the degree of tumour cell proliferation [22] had limited utility in predicting tumour behaviour. Well documented malignant transformation in benign GCT can occur following radiotherapy [23, 24]. To our knowledge, there has been only one primary malignant GCT reported in the skull in a patient with Paget's disease [15]. Histological features of malignant change may be only focal and include atypical mononuclear cells together with abnormal mitotic figures. Patients with malignant GCT have a poor prognosis and most die within 1 year [15, 24].

Optimal treatment for both GCT and CGCG is surgical resection with post operative radiotherapy if primary excision is considered to be incomplete. Surgical reconstruction maybe considered if wide primary excision has been necessary. Curettage alone has been associated with higher recurrence rates [5, 6]. The risk of malignant transformation following radiotherapy has decreased significantly since orthovoltage radiation has been largely replaced by megavoltage radiation [5, 10]. Chemotherapy is usually reserved for those cases which remain inadequately controlled by surgery and irradiation and often consists of a combination regimen of methotrexate, adriamycin and cyclophosphamide [10, 11].

Conclusion

Giant cell lesions of the skull occur rarely and most arise in the jaw bones, the sphenoid and temporal bones. The most difficult differential diagnosis lies between GCT of bone and CGCG. There appear to be some cases with distinct histological features of either GCT or CGCG, however these lesions are indistinguishable radiologically and there may be considerable overlap in the microscopic appearances. Our case report demonstrated one such borderline lesion, although with more features of a GCT than a CGCG. With present knowledge it appears that both GCT and CGCG of the skull are best treated by complete surgical excision with adjuvant radiotherapy if primary removal was not possible. There are controversial opinions about whether GCT of the skull may be more similar to CGCG than GCT of the long bones in behaviour and prognosis. Further research including molecular genetic investigations may be required to address this problem and test the hypothesis that CGCG and GCT represent two ends of a disease spectrum.

Acknowledgements The histological slides were prepared in the Laboratory at Department of Clinical Neuropathology, King's College Hospital, London, UK.

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