

Case report

Title of paper:

Frontal skull osteoblastoma with aneurysmal bone cyst-like changes associated with trauma during pregnancy: a case report

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Abstract:

We report the case of a large osteoblastoma arising in the frontal bone of a 20 year-old female. The lesion was first noted after a fall, and grew steadily in size following further head injury during pregnancy. Initial plain radiography demonstrated an area of radiolucency, with subsequent cross-sectional imaging revealing the extent of the lesion. Following successful surgical resection, histological features were suggestive of an aggressive osteoblastoma with aneurysmal bone cyst-like changes. We consider the influence of pregnancy and trauma on osteoblastoma behaviour.

Keywords:

Osteoblastoma; aneurysmal bone cyst; pregnancy; trauma

Introduction

Osteblastomas account for approximately 1% of all bone tumours, with only 4% of these arising from the calvarium [23]. Osteblastomas behave as benign lesions, although aggressive osteoblastoma is a term used to describe lesions that show atypical cytological features which may be correlated with recurrence, often making differentiation from other entities such as osteoblast-like osteosarcoma difficult. Associated aneurysmal bone cysts (ABC) are seen in up to 10% of osteblastomas [23]. The aetiopathogenesis of ABCs remains poorly understood, and our case demonstrates predisposing factors to the development of an ABC. To the best of the authors' knowledge, this is the first report in the literature of a coexistent aggressive osteoblastoma with ABC-like changes occurring in pregnancy, with the additional precipitant of repeated head trauma. We consider the interplay between these various factors in this clinical case report.

Case Report

History & Presentation

Following a fall, a 20 year old lady presented to her local emergency department, where plain skull radiography revealed a prominent lytic area in the right frontal bone with a well-defined clear margin measuring approximately 5.5cm (Figure 1a). The swelling remained static in size until she suffered a second episode of minor head trauma about nine months later. At the time of the second injury, she was 7 months pregnant. The swelling subsequently increased in size to approximately 7.5x6cm when she presented with headaches, nausea and vomiting one month after parturition. On examination, there was tenderness on palpation of the frontal swelling, no neurological deficit or papilloedema. Laboratory investigations revealed an elevated serum alkaline phosphatase level.

Pre-operative CT and MR imaging demonstrated a large well-demarcated solitary frontal heterogeneous multi-cystic intra-osseous lesion with mass effect, causing underlying brain distortion but little surrounding reactive response (Figure 1b,c). There

was no soft tissue overlying the lesion, nor any surrounding inflammatory changes. The bone cortex was intact but thinned and there were areas of central dystrophic calcification. Differential diagnoses on initial review of imaging included haemangiopericytoma, atypical intra-osseous meningioma, calvarial osteosarcoma, fibrous dysplasia and histiocytosis.

Operation & Post-operative Course

Intra-operatively, there was a protruding portion of skull bone with diameter of 100mm, and thickness of 8mm (Figure 2). The outer surface had a vesicular 16 mm defect, through which herniated an internal tumour measuring 60 x 60 mm. The tumour had a fleshy appearance, and was adherent to underlying dura mater. Gross total resection was achieved with a 1cm margin.

Histological analysis (Figure 3) showed a bone forming tumour composed of diffusely anastomosing trabeculae of woven bone and osteoid, lined by a row of activated osteoblasts with no evidence of cellular atypia. The intervening loose fibrovascular stroma was scattered with osteoclasts, and there were large blood-filled cystic spaces. The diploe was expanded by tumour, with a crisp cortical-periosteal reaction, but there was no evidence of host bone permeation or any other features of malignancy. The oestrogen (ER) and progesterone (PR) receptor assays were negative. At 2-year post-operative follow up, the patient remained tumour-free.

Discussion

First described in 1932 [12], the current term osteoblastoma was independently proposed by Jaffe and Lichtenstein in 1956 [10,16], as an osteoid tissue-forming primary neoplasm of bone sharing clinical and histological features with osteoid osteoma. Osteoblastomas most commonly affect the posterior spinal elements, but arise from the cranium in 13-21% of cases [23]; only 2-4% of all osteoblastomas arise from the calvarium, with temporal, frontal and ethmoid bones being most commonly affected. They occur more commonly in patients under the age of 30, with a recognised male predilection, which is reportedly reversed in the case of extra-

calvarial osteoblastomas [1]. Progressive painful swelling, unrelieved by non-steroidal anti-inflammatory drugs, is the most frequent clinical presentation. Other clinical features of skull osteoblastomas are signs of raised intracranial pressure, cranial nerve deficits related to location (e.g. hearing loss, tinnitus, facial palsy), seizures and malignant transformation in less than 1% of cases [23].

Histologically, osteoblastomas are bone-forming tumours composed of anastomosing trabeculae of osteoid and woven bone lined by a layer of activated osteoblasts [WHO 2013 ref]. They mostly behave as benign tumours, but the pathologic entity of 'aggressive osteoblastoma' has been described [17] for variants of osteoblastoma with features encroaching on that of the malignant tumour osteosarcoma. Subsequent terms of 'pseudomalignant osteoblastoma' and 'malignant osteoblastoma' later emerged, with further suggestion that aggressive osteoblastoma is really an osteoblastoma-like osteosarcoma [18]. Such borderline tumours can be extremely difficult to differentiate [2]; the main distinguishing features being cellular atypia and permeation with osteodestructive growth into host bone.

Indeed, an osteoblastoma-like osteosarcoma was a diagnostic consideration in this case given the patient's history of rapid tumour growth and the lesion's radiographic appearance. Ultimately the lack of malignant histological features (necrosis, permeation into host bone and cellular atypia) in the sample made this diagnosis less likely. Another bony tumour which is exceedingly common in the frontal sinus is an osteoma with osteoblastoma-like features. Again, these tumours can be focally very difficult to differentiate from a pure osteoblastoma. They are composed primarily of dense, compact (so-called 'ivory') or trabecular (so-called 'mature') bone and a paucicellular stroma. Key differences between this entity and osteoblastoma are that there is little in the way of osteoblastic rimming, much more mature bone formation and marked Pagetoid changes indicating intense bone remodelling.

The term aneurysmal bone cyst (ABC) was coined in 1942 [11] to describe a bone lesion with a vascular lining and a characteristic 'soap-bubble' roentgenographic appearance of expanded bone. More common in patients under the age of 20, with a slight female preponderance, only 3-6% of ABCs arise from the cranium [3].

ABCs are described as primary when they arise *de novo* in healthy bone tissue. In recent years, cytogenetic abnormalities have been implicated in the development of such lesions by a mechanism of abnormal chromosomal translocation affecting the USP6 gene [15]. ABCs are described as secondary when they arise within primary bony lesions, such as osteoblastomas. In the case presented here, exposure to trauma [24], causing haemorrhage and aberrant vascular proliferation, predisposed to the development of a secondary ABC, exhibited in the histological sample by large blood-filled cystic spaces with intervening fibrovascular stroma and scattered osteoclasts [WHO 2013 ref]. The association between head trauma and osteolytic skull lesions – creating a favourable cellular milieu for ABC formation – has been well-described [6,7,9]. As they contain a multitude of cell types, it has been postulated that ABCs represent a restorative reaction to this insult [21]. Moreover, there are several reports of ABCs arising in pre-existing lesions during pregnancy [17], or arising *de novo* and growing significantly during pregnancy [8].

The trophic effects of oestrogen on bone are well-established [14]. This steroid hormone acts by direct and indirect binding to the oestrogen receptor; both alpha and beta subtypes have been found to be expressed in osteoblasts, but are notably absent from ABCs [4]. Circulating oestrogen levels rise during pregnancy, therefore the gravid state certainly has the potential to precipitate progression of bone tumour.

To the best of the authors' knowledge, there is only one case report of osteoblastoma presenting in pregnancy, although in this report, recurrence was not temporally associated with pregnancy itself. Gertzbein and colleagues [5] describe a recurrent osteoblastoma of the second thoracic vertebra in a 26 year-old female, who first presented whilst in late pregnancy. Despite complete resection of the histologically-confirmed osteoblastoma, with good neurological recovery, paraparesis returned five and a half years later. Imaging confirmed recurrence of a large, partly calcified tumour in the left upper thorax, which was again completely resected. Histological features of the recurrent tumour showed increasing maturation of a benign osteoblastoma.

There is a paucity of literature regarding the association of bone tumours with pregnancy, and many reports discuss more aggressive bone tumours such as sarcomas [19,22]. A retrospective study of 33 pregnant women studied the effect of pregnancy on the behaviour of a variety of primary bone malignancies [25]. The

authors concluded that pregnancy has no effect on the clinical behaviour of bone sarcomas, although this assertion is tempered by the subjective, questionnaire-based methods, which yielded equivocal results. More recently, Israeli investigators retrospectively studied a cohort of women diagnosed with bone or soft tissue sarcomas, finding that even with postpartum deferral of definitive oncological treatment, the malignancy did not adversely affect the pregnancy [22]. All subjects in an earlier paper by the same group [19] reported disease progression during pregnancy, but it is not possible to ascertain if progression was more swift than in non-gestational counterparts without a direct control group.

In the case described above, the patient likely already had a slow-growing osteblastoma at the time of the first trauma. Subsequent convergent factors of pregnancy (with attendant trophic hormonal effects on bone) and repeated trauma to the site likely caused rapid increase in the size of the lesion, most likely by a mechanism of bleeding and secondary ABC formation. There is precedent in the literature for trauma as a trigger for development of osteolytic bone lesions, including ABCs and osteblastomas, and well-described transformations of benign osteblastomas into more aggressive forms. However, the role and mechanism of pregnancy in perpetuating this abnormal bone growth is unclear. Pregnancy may be overlooked as a contributing factor to progression of bony tumours, which should be carefully monitored in the gravid state to avoid patients coming to emergent neurosurgical attention.

References

1. Aziz TZ, Neal JW, Cole G: (1993) Malignant osteoblastoma of the skull. *Br J Neurosurg* 7:423–6
2. Dorfman HD, Weiss SW: (1984) Borderline osteoblastic tumors: problems in the differential diagnosis of aggressive osteoblastoma and low-grade osteosarcoma. *Semin Diagn Pathol* 1:215–34

3. Gan Y-C, Hockley AD: (2007) Aneurysmal bone cysts of the cranium in children. Report of three cases and brief review of the literature. *J Neurosurg* 106:401–6
4. Garber ST, Riva-Cambrin JK: (2015) Occipital aneurysmal bone cyst rupture following head trauma: case report. *J Neurosurg Pediatr* 15:272–275
5. Gertzbein SD, Cruickshank B, Hoffman H, Taylor GA, Cooper PW: (1973) Recurrent benign osteoblastoma of the second thoracic vertebra. A case report. *J Bone Joint Surg Br* 55:841–7
6. Hećimović I, Dmitrović B, Rubin O, Rukovanjski M, Vranković D: (1999) Skull osteolysis after mild head trauma: case report. *Surg Neurol* 51:43–6
7. Hermann EJ, Hong B, Brandis A, Krauss JK: (2011) Progressive osteolytic calvarial lesions in children after minor head injury. *Pediatr Neurosurg* 47:133–7
8. Hnenny L, Roundy N, Zherebitskiy V, Grafe M, Mansoor A, Dogan A: (2015) Giant Aneurysmal Bone Cyst of the Anterior Cranial Fossa and Paranasal Sinuses Presenting in Pregnancy: Case Report and Literature Review. *J Neurol Surg reports* 76:e216–21
9. Hornig GW, Beatty RM: (1990) Osteolytic skull lesions secondary to trauma. Report of two cases. *J Neurosurg* 72:506–8
10. Jaffe HL: (1956) Benign osteoblastoma. *Bull Hosp Joint Dis* 17:141–51
11. Jaffe H, Lichtenstein L: (1942) Solitary unicameral bone cyst with emphasis on the roentgen picture, the pathologic appearance, and the pathogenesis. *Arch Surg* 44:1004–25
12. Jaffe H, Mayer L: (1932) An Osteoblastic Osteoid tissue-forming tumor of a metacarpal bone. *Arch Surg* 24:550–564
13. Kransdorf MJ, Sweet DE: (1995) Aneurysmal bone cyst: concept, controversy, clinical presentation, and imaging. *AJR Am J Roentgenol* 164:573–80
14. Krassas GE, Papadopoulou P: (2001) Oestrogen action on bone cells. *J Musculoskelet Neuronal Interact* 2:143–51
15. Lau AW, Pringle LM, Quick L, Riquelme DN, Ye Y, Oliveira AM, Chou MM: (2010) TRE17/ubiquitin-specific protease 6 (USP6) oncogene translocated in aneurysmal bone cyst blocks osteoblastic maturation via an autocrine mechanism involving bone morphogenetic protein dysregulation. *J Biol Chem* 285:37111–20
16. Lichtenstein L: (1956) Benign osteoblastoma; a category of osteoid-and bone-forming tumors other than classical osteoid osteoma, which may be mistaken for giant-cell tumor or osteogenic sarcoma. *Cancer* 9:1044–52

17. Lucas DR, Unni KK, McLeod RA, O'Connor MI, Sim FH: (1994) Osteoblastoma: clinicopathologic study of 306 cases. *Hum Pathol* 25:117–34
18. Lypka MA, Goos RR, Yamashita D-DR, Melrose R: (2008) Aggressive osteoblastoma of the mandible. *Int J Oral Maxillofac Surg* 37:675–8
19. Merimsky O, Inbar M, Issakov J, Kollender Y, Flusser G, Meller I, Bickels J: (2003) Gestation-related malignant musculoskeletal tumors. *Isr Med Assoc J* 5:264–7
20. Mintz MC, Dalinka MK, Schmidt R: (1987) Aneurysmal bone cyst arising in fibrous dysplasia during pregnancy. *Radiology* 165:549–50
21. Mirra J, Picci P, Gold R: (1989) Cysts and cyst-like lesions of bone. In: Mirra JM (ed) *Bone tumors: clinical, radiologic and pathologic correlations*. Lea & Feibiger, USA, pp 1233–1334
22. Molho RB, Kollender Y, Issakov J, Bickels J, Flusser G, Azem F, Alon, A, Inbar MJ, Meller I, Merimsky O: (2008) The complexity of management of pregnancy-associated malignant soft tissue and bone tumors. *Gynecol Obstet Invest* 65:89–95
23. Pelargos PE, Nagasawa DT, Ung N, Chung LK, Thill K, Tenn S, Gopen Q, Yang, I: (2015) Clinical characteristics and diagnostic imaging of cranial osteoblastoma. *J Clin Neurosci* 22:445–9
24. Rapp TB, Ward JP, Alaia MJ: (2012) Aneurysmal bone cyst. *J Am Acad Orthop Surg* 20:233–41
25. Simon MA, Phillips WA, Bonfiglio M:(1984) Pregnancy and aggressive or malignant primary bone tumors. *Cancer* 53:2564–9

Informed Consent

Informed consent was obtained from the participant included in the study.

Conflicts of Interest

The authors disclose no conflicts of interest in submitting this manuscript.

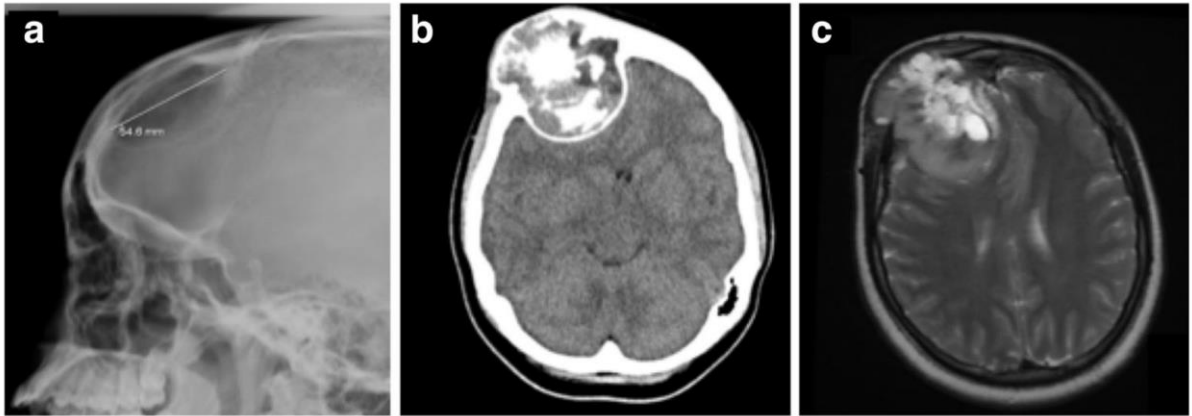


Fig. 1 Pre-operative imaging. **a** plain skull radiography on index presentation; **b** axial CT imaging; **c** axial T2-weighted MR imaging, both taken 9 months later.



Fig. 2 Intra-operative photograph showing reflected bicoronal scalp flap (upper) and rounded, protuberant bony lesion (lower), with scale marker.

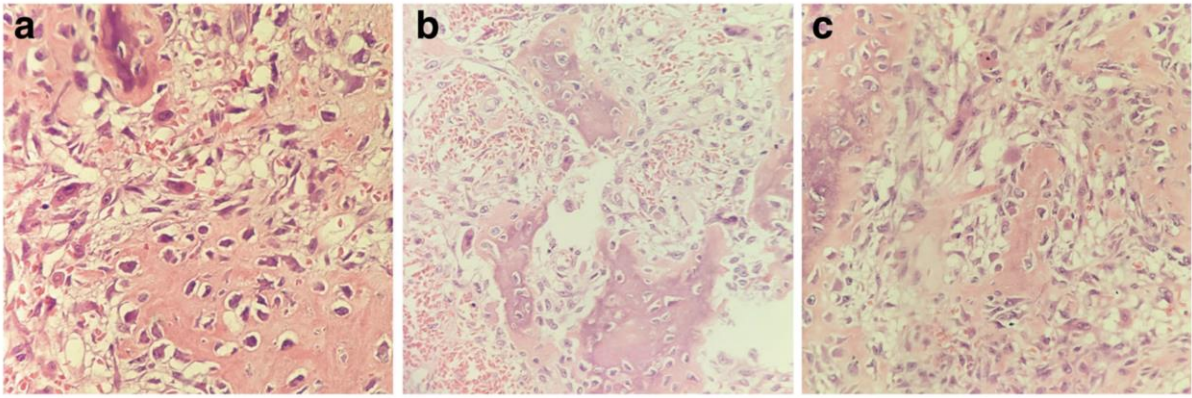


Fig. 3 Haematoxylin and eosin-stained tissue sample at 20-fold magnification. See text for description.