Journal of Clinical Orthopaedics and Trauma 59 (2024) 102825

Contents lists available at ScienceDirect

Journal of Clinical Orthopaedics and Trauma

journal homepage: www.elsevier.com/locate/jcot

Original article

Measurable progression of giant cell tumour of bone associated with pregnancy - A tertiary sarcoma centre analysis

Henderson RD[a,*], Shirodkar K[a], Hussein M[a], Jenko N[a], Jeys L[b], Botchu R[a]

[a] Department of Musculoskeletal Radiology, Royal Orthopaedic Hospital, Birmingham, UK
[b] Department of Orthopaedic Oncology, Royal Orthopaedic Hospital, Birmingham, UK

ARTICLE INFO

Keywords:
Giant cell tumour of bone
Pregnancy
Postpartum
Recurrence
Progression
Hormonal influence

ABSTRACT

Introduction: Giant cell tumour of bone (GCTB) is a benign but locally aggressive bone tumour with a higher predilection for females of reproductive age. GCTB management poses a unique set of challenges during pregnancy due to risks associated with imaging and treatment options. Pregnancy has been implicated in GCTB progression and tumour recurrence, however an exact mechanism has not been established. This study aims to confirm the relationship between the diagnosis and progression of GCTB during pregnancy.

Methods: A 17-year retrospective analysis of our tertiary sarcoma referral centre database was performed to identify the relevant patients. Pregnancy-associated tumours were defined by those already present or diagnosed during pregnancy, and up to 12 months postpartum. Lesion volume was determined by mathematical ellipsoidal modelling technique to simplify the estimation, with cross-sectional measurements obtained from the three standard orthogonal planes on initial and surveillance imaging. Due to logistical challenges, follow-up imaging was performed at either our tertiary sarcoma centre or under guidance at regional imaging centres convenient to the patient.

Results: The diagnosis of GCTB was made in 113 female patients during this 17-year period, of which 20 were associated with pregnancy with a mean age of 28.8 years (range 19–40 years). 12 patients had their primary or recurrent GCTB diagnosed, or known tumour progress during pregnancy, whilst the remaining 8 were diagnosed shortly thereafter to within 12 months postpartum. The most common tumour sites were located around the knee (30 %) and distal radius (25 %). A statistically significant pattern of growth was observed through the surveillance period (p 0.018), within a relatively short mean follow-up period of only 89.8 days (SD 54.5; 13–192 days).

Conclusion: This study demonstrates the significant association that pregnancy has with the growth and progression of both primary and recurrent GCTB. Pregnant patients should be subject to close surveillance well into the postpartum period due to possible accelerated disease progression and potential for disease recurrence.

1. Introduction

Giant cell tumour of bone (GCTB) is a benign but locally aggressive bone tumour and despite highly precise intralesional curettage or marginal excision, they can recur.

GCTB most often involve the distal femur, proximal tibia and distal radius. They typically develop in young adults following growth plate closure, where 80 % of lesions developing between 20–50 years of age, with a particular propensity for reproductive-age females peaking between 20–30 years old, whilst children and older adults are less likely to be affected.[1–3]

Physiological changes during pregnancy can complicate the diagnosis and treatment for giant cell tumour of bone.[4,5] Despite extensive analysis and investigation, the exact mechanism and underlying hormonal association of GCTB has not been established[5] despite the implication in a sometimes unpredictable and aggressive disease progression or recurrence.[6–9]

The diagnostic and management options are also restricted by potential implications on the mother's health and the safety of exposing the fetus to ionising radiation and high magnetic fields. Conventional radiographs and computed tomography (CT) are used sparingly or in exceptional circumstances during pregnancy to reduce antenatal

* Corresponding author. Royal Orthopaedic Hospital Bristol Road South, Northfield, Birmingham, UK.
E-mail address: hendo.rd@gmail.com (R. Henderson).

https://doi.org/10.1016/j.jcot.2024.102825
Received 30 April 2024; Received in revised form 26 October 2024; Accepted 14 November 2024
Available online 17 November 2024

ionising radiation exposure.[4,10]

This study aims to confirm the relationship between the diagnosis and progression of GCTB during pregnancy.

2. Methods

The study sample was derived from the patients attending a tertiary orthopaedic oncological service for the management of their primary and recurrent GCTB. Following institutional body approval, a retrospective search between the years 2006 and 2023 was performed on the digital oncological database for the Royal Orthopaedic Hospital NHS Foundation Trust in Birmingham, UK. Three key data points were employed to identify the subjects across this 17-year period; this included search parameters included terms '*GCT*' and '*giant cell tumour*', female, and pregnancy. Male patients and lesions without confirmed histopathological diagnosis of GCTB were excluded.

Pregnancy-associated tumours were defined by a diagnosis made during pregnancy and including up to 12 months postpartum. The definition was essential to accurately identify and analyse cases of GCTB occurring in the context of pregnancy.

The diagnostic workup included the initial targeted radiograph with subsequent diagnostic evaluation with multiplanar multisequence MR imaging. Baseline cross-sectional dimensions of the lesion (in millimetres) were measured in the standard three orthogonal planes transverse (TV), anteroposterior (AP) and craniocaudal (CC). This was achieved on the PACS workstation and image-viewing software package (Centricity Universal Viewer, GE) by a fellowship-trained consultant musculoskeletal radiologist. Lesion volume was then determined by mathematical ellipsoidal modelling technique ($V = 4/3\pi$*abc) to simplify the volumetric estimation.

Surveillance imaging for both pregnant and postpartum patients was ideally performed with MRI. However, on account of feasibility, local resource availability and accessibility or MRI safety concerns (especially early pregnancy), follow-up imaging was performed radiographically with comparison to both the original diagnostic radiograph and MRI. This was especially relevant during the calendar years of 2021–2022, where an international epidemic impacted the surveillance of 3 patients.

3. Results

During the 17-year search period a total of 122 patients were identified from the oncological database search terms '*GCT*' and '*giant cell tumour*'. This cohort comprised 113 female patients with mean age of 27.7 years (range 15–46 years), of which 20 cases (21.5 %) with mean age 28.5 years (19–40 years) were associated with pregnancy.

From the pregnancy-associated patient subgroup we identified 13 cases (65 %) where either a primary diagnosis, recurrence of previously treated GCTB, or known GCTB progressed during pregnancy [Fig. 1]. The remaining 7 cases (35 %) had symptoms manifest or deteriorate during the course of their pregnancy however the primary GCTB or disease recurrence was only diagnosed postpartum.

The most common tumour sites associated with pregnancy (n = 20)

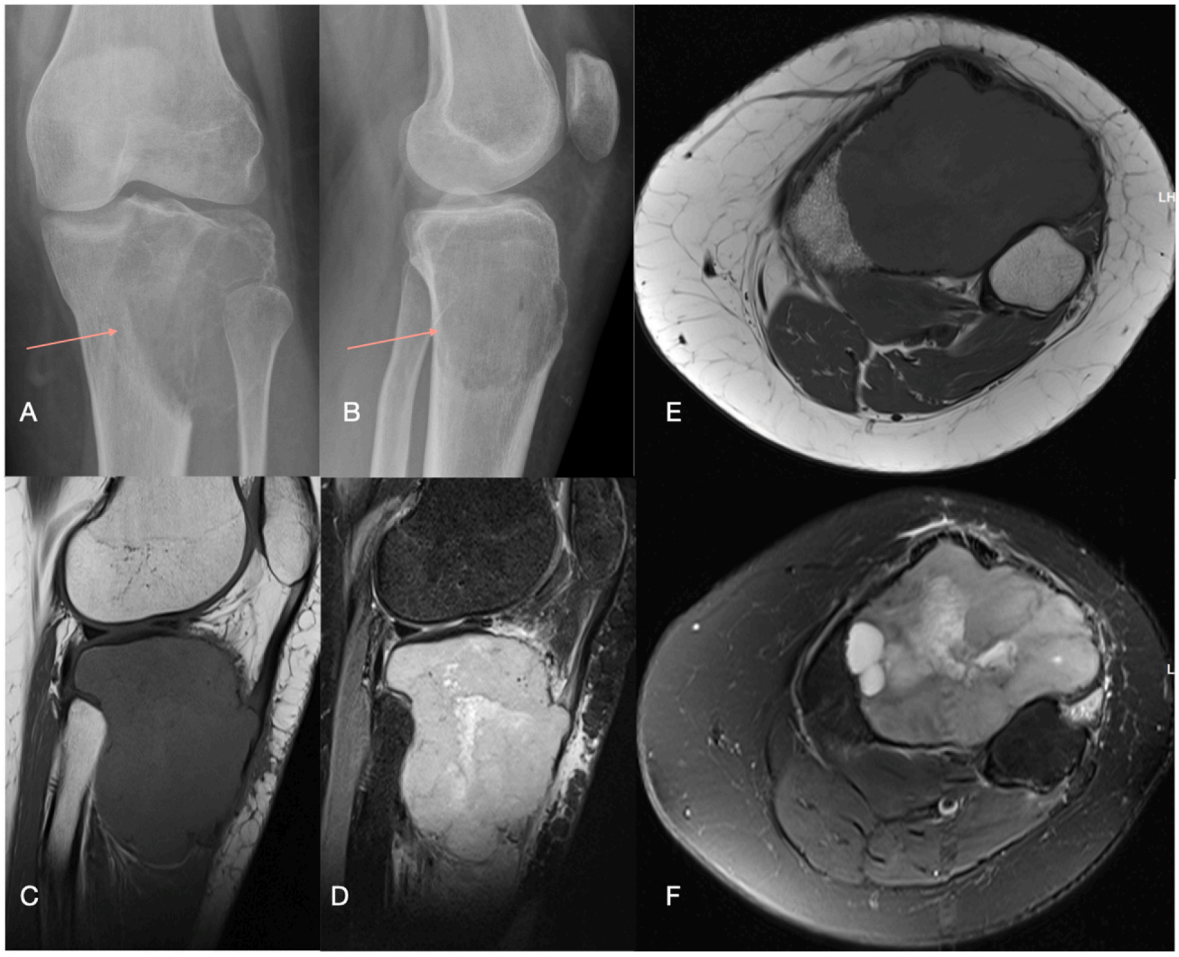

Fig. 1. A–F: (A) Frontal radiograph showing a well-circumscribed, expansile and osteolytic lesion in the left proximal tibia with extension to the subarticular bone plate in keeping with GCTB; (B) Lateral radiograph further characterising the expansile osteolytic lesion; (C) T1-weighted sagittal and (E) axial MR images showing homogenous intermediate signal expansile mass in the proximal tibia with subarticular extension; (D) Short tau inversion recovery (STIR) sagittal and (F) axial images showing heterogeneous intermediate-high signal. No extraosseous component evident.

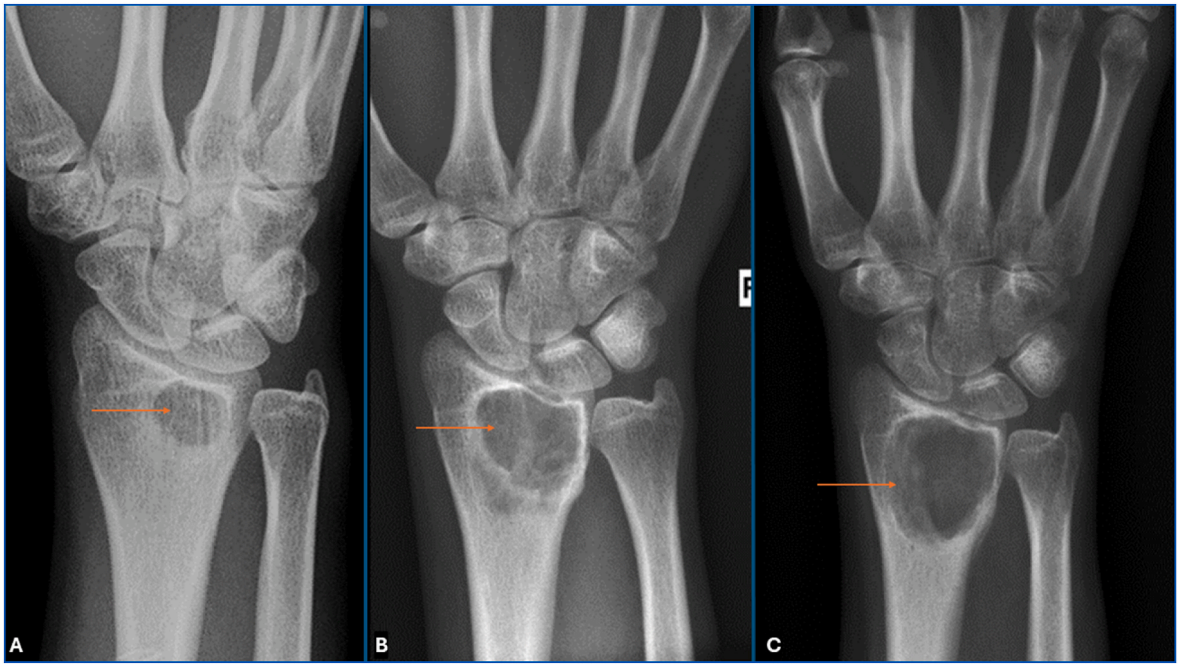

Fig. 2. A–C: Progressive increase in both size and subarticular extension in this distal radius GCTB through serial imaging from (A) initial diagnostic radiograph, (B) through pregnancy and finally (C) postpartum. Radiographic progression corresponded with symptom deterioration through this period.

were 6 lesions (30 %) located at the knee (distal femur, proximal tibia), 5 lesions (25 %) in the distal radius, 3 lesions (15 %) in the distal tibia, 2 lesions (10 %) in the sacrum, and single (5 %) in each of the proximal humerus, hand, proximal femur and foot. For comparison, distribution of tumour sites in other non-pregnant female cohort (n = 73) were recorded, with the most common location the knee with 33 lesions (45 %) plus an additional 5 lesions in the proximal fibula (7 %), pelvis and sacrum 14 lesions (19 %) and distal radius with 5 lesions (7 %) [Figs. 2 and 3].

Five cases (25 %) of pregnancy-associated GCTB represented recurrent disease, which twice involved the distal tibia, and one instance for each of the proximal humerus, proximal tibia and foot.

At presentation the mean volume was 43.8 cm^3 (SD 49.8) with a mean follow-up time of 89.8 days (SD 54.5; range 13–192 days). There was an overall mean increase of 11.5 cm^3 (SD 14.4) or 65.5 % (SD 96.3 %; range 3.1–348 %) with a statistically significant pattern of growth

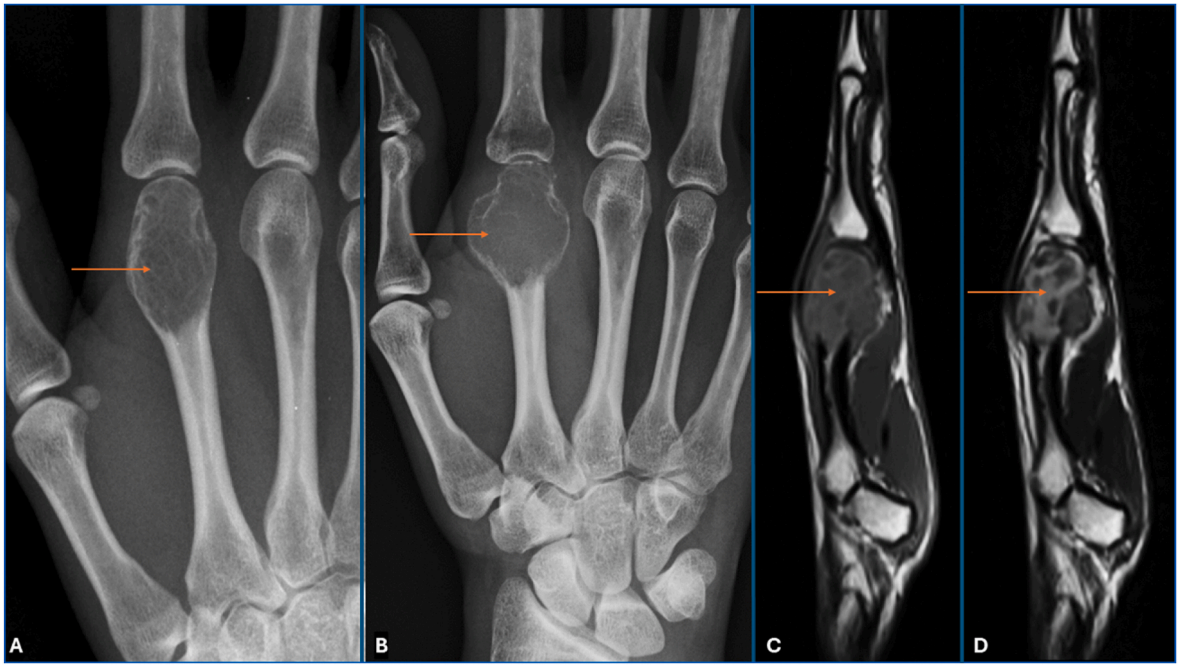

Fig. 3A. A–D: (A) Frontal radiograph of the hand showing the characteristic bubbly expansile osteolytic lesion in the distal 2nd metacarpal with subarticular extension; (B) progressive predominantly transverse fusiform expansive growth over a 3-month period, with cortical thinning plus irregular articular margin at the metacarpal articular head at the ulnar aspect; (C,D) Sagittal MRI sequences showing minimally heterogeneous T1 (C) and mixed intermediate-high T2 (D) signal soft tissue mass involving the distal third of the 2nd metacarpal with subarticular extension. Lesion remains bound by intact periosteum.

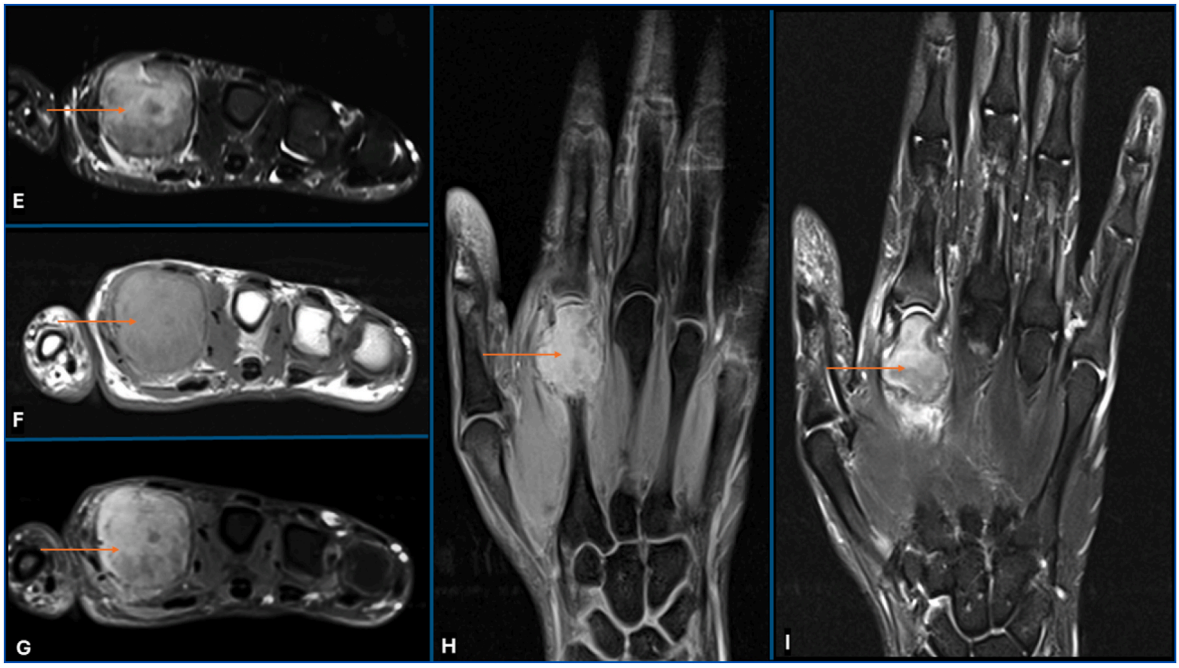

Fig. 3B. E–I: Axial MR images further characterising the expansile soft tissue mass with mottled heterogeneous T2 turbo inversion recovery magnitude (TIRM) (E), T1 (F), and T1 fat-saturated (FS) (G). Lesion is contained by the intact periosteum. Small halo of soft tissue oedema in the surrounding intrinsic hand structures; (H,I) coronal T1 FS (H) and T1 TIRM (I) sequences showing distal subarticular extension. The patient subsequently underwent intrapartum curettage and bone grafting.

observed through the surveillance period (p 0.018) on *t*-test [Fig. 4].

In one instance where diagnosis of GCTB had been made, the noticeable symptomatic progression would in retrospect coincide with conception and the few early weeks of pregnancy. Intralesional curettage and bone allograft was performed in the early first trimester period without complication. The patient would unfortunately however experience postpartum disease recurrence requiring subsequent wrist fusion augmented with fibular strut autograft.

Similarly, where because of the significant deterioration in their symptoms, a patient had opted for termination of pregnancy and despite undergoing intralesional curettage and bone allograft shortly thereafter, would develop recurrent disease within the 12-month post-pregnancy

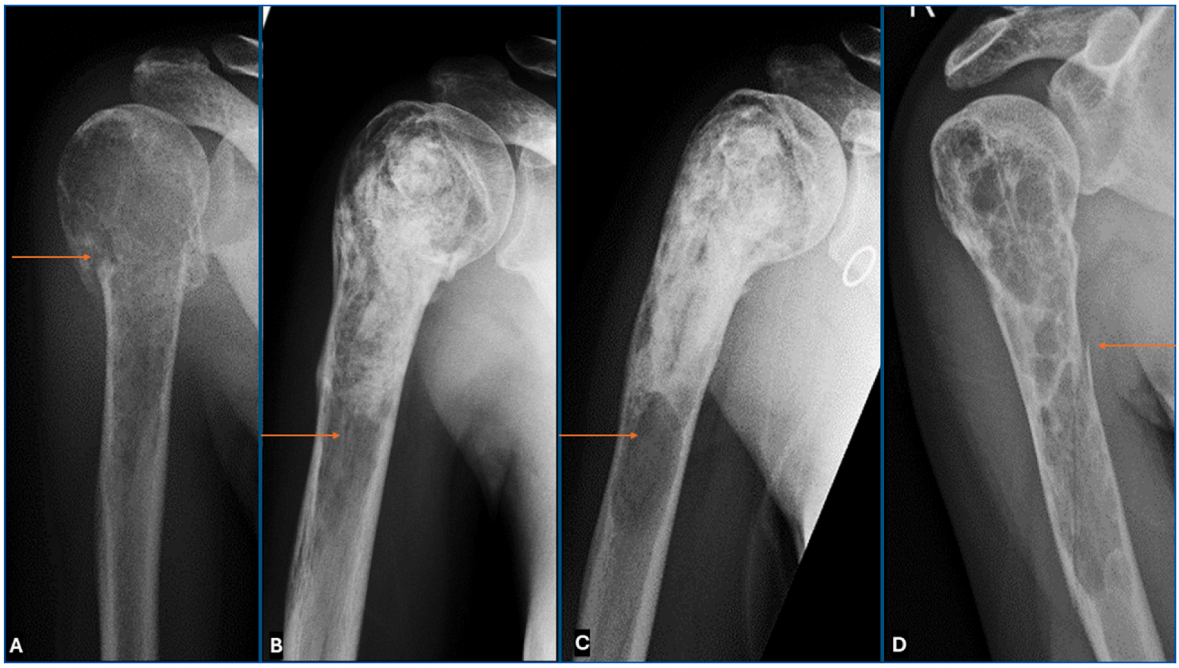

Fig. 4. A–D: (A) Initial diagnostic frontal radiograph of the right humerus identifies an expansile osteolytic lesion with faint bubbly architecture encroaching on the humeral head subarticular bone. Surgical neck of humerus is undermined by endosteal scalloping and cortical thinning which has been complicated by minimally-displaced pathological fracture; (B) Post-intralesional curettage and bone grafting; (C) Postpartum radiograph demonstrates well-circumscribed osteolytic lesion localised to the distal bone-graft interface highly suspicious for recurrence; (D) After an extended period lost to follow-up, the patient returned over 12 months postpartum when extensive recurrence has replaced the bone graft material and further complicated by pathological fracture.

window prior to commencement of denosumab therapy.

In the tragic instance where a patient suffered a miscarriage in the early second trimester, there was still a measurable size increase observed on subsequent imaging.

In the early postpartum period a total of 5 patients were commenced on denosumab therapy, with measurable disease progression still observed in 2 cases who then underwent surgical intervention.

For one patient suffering recurrent GCTB associated with pregnancy, a worldwide pandemic compounded already challenging domestic circumstances. Following measurable growth during her postpartum surveillance period she was lost to follow-up for an extended period of time. She would unfortunately return with significant disease progression again complicated by pathological fracture [Fig. 5].

4. Discussion

Pregnancy-associated tumours are defined as being diagnosed during pregnancy or within the postpartum period. There are few tumours with a recognised link and relative predilection for pregnancy, with the most common being breast, haematological and melanoma being the most common.[11] Not only associated with pregnancy, there is also a recognised pattern of accelerated and aggressive GCTB growth and recurrence,[6–9] however the exact causal mechanism has not yet been established.[5,10]

Our cohort demonstrated sites of tumour disease similar to that documented in the literature, with the highest incidence located around the knee (distal femur and proximal tibia; 30 %). The next most common sites at the distal radius, sacrum and proximal humerus were similarly consistent with the general population.[2] This was also consistent for the non-pregnant female cohort.

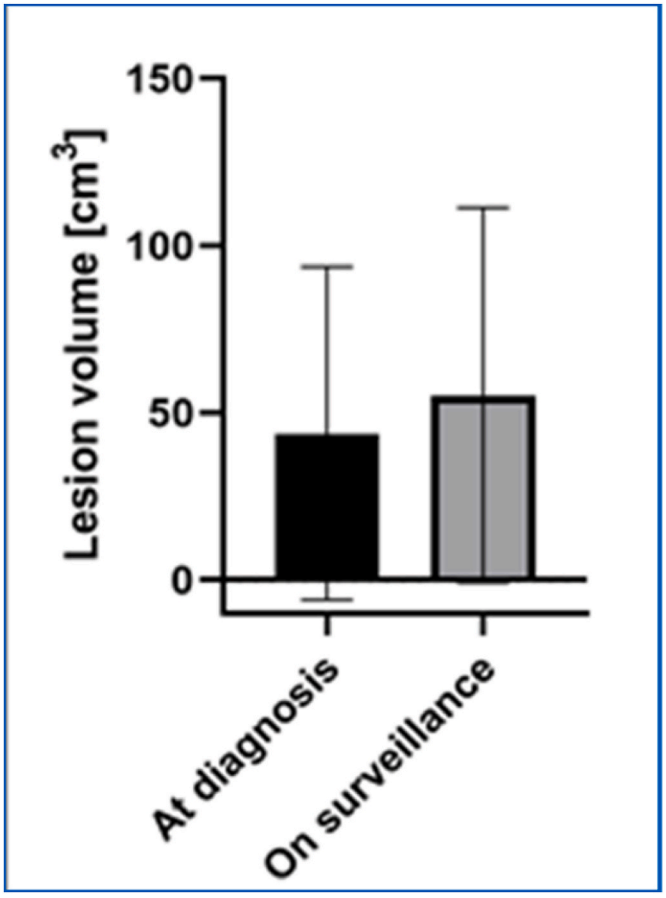

Fig. 5. Paired *t*-test demonstrating statistical significance of GCTB growth through the surveillance period.

Malignant transformation is possible, although rare, occurring in 1–2% of cases,[2,12] with reports as high as 5 %,[13] with a recognised increased incidence in males. Although metastatic GCTB has been reported during pregnancy in the descriptive literature, we report no cases in our cohort.

In isolation, the management of bone and soft tissue tumours alone is a complicated process requiring interdisciplinary involvement. There is then understandably added layers of complexity and precaution when tumours are identified in pregnant and postpartum patients.

There is a recognised shift in the behaviour of GCTB during pregnancy, with a shift toward an unpredictable and aggressive pattern of disease progression and recurrence. Discussions have emerged proposing explanations for this altered behaviour, with the idea of GCTB being influenced by hormonal regulation through oestrogen (ER) and progesterone receptor (PR) expression,[14–16] and as such the elevated physiological levels of these hormones will influence tumour biology and causal for the aggressive behaviour and pattern of growth.

GCTB typically occur in young adults following skeletal maturity and growth plate closure, with higher predilection for females at reproductive age (1:1.2–1.7, male:female), with peak incidence at 20–30 years of age.[1–3] The exact cause for the preferential female incidence remains unclear although hormonal influence has been raised, however it warrants further investigation to unearth its significance and the potential implications for ongoing GCTB management.[7,10]

The onset and progression of symptoms was reported throughout all stages of pregnancy and corresponded to measurable increase in tumour size during surveillance well into the postpartum period. In retrospect the reported onset or increase of symptoms in 3 cases can be correlated to the early pregnancy period (first trimester post-conception), with pregnancy then confirmed in the subsequent months.

The management of one particular case of GCTB recurrence reported during pregnancy already discussed, complicated by challenging social circumstances where she was lost to follow-up and planned surgical intervention for an extended time. On reassessment over 12 months later, there had been substantial progression of the recurrent disease and then complicated by minimal-trauma pathological fracture. Recurrent GCTB deterioration in this instance required en bloc surgical resection and endoprosthetic replacement of the proximal humerus.

Interestingly, the physiological influence can even persist beyond an incomplete pregnancy. There was demonstrable GCTB growth observed following both an early elective first-trimester pregnancy termination, and two unfortunate cases of spontaneous miscarriage; one in the late first trimester and other in early second trimester.

The treatment decisions compete against heightened anxieties whilst balancing optimal maternal health and fetal outcomes, which present considerable obstetric and orthopaedic surgical challenges. There are often delays to diagnosis, with many vague, non-specific and minor symptoms either masked, dismissed or misinterpreted as the ‘normal’ aches and discomforts attributed to pregnancy.[17] As with many other tumours, delayed diagnosis is associated with poorer prognosis.[12,18,19]

Escalating oncological surgical interventions has formed the bedrock of GCTB surgery for decades, with techniques including intralesional curettage, marginal excision and finally en block resection with surgical reconstruction. Orthopaedic surgery and general anaesthetic however are unfortunately not without their risks to either mother or developing fetus.

The standard non-operative treatment for GCTB is biological denosumab therapy, a fully human monoclonal antibody directed against receptor activator of nuclear factor-κB ligand (RANK-L).[20]

The advent of denosumab has improved outcomes for GCTB through inducing tumour consolidation, overall reduced tumour burden whilst delivering significant symptomatic relief.[19,20] This treatment however is contraindicated in pregnancy due to potential teratogenic effects through impaired fetal bone growth and neonatal hypocalcaemia. Although there have been instances of successful pregnancies carried to full term whilst on denosumab therapy in the descriptive literature,

healthcare practitioners continue to advise female patients under treatment to employ contraceptive techniques and avoid pregnancy.

Should surgical intervention not be performed immediately or even at all during pregnancy, unfortunately for this specific cohort denosumab remains contraindicated. This situation delivers a unique opportunity for possible tumour surveillance and observation of behaviour change during pregnancy. Some alternative management options might then include.

1. Surgical management: performing GCTB intralesional curettage following rigorous risk-benefit analysis and involvement of a specialist oncological orthopaedic surgeon to optimise maternal safety and minimise fetal harm.
2. Embolisation: should surgery be determined unfavourable, especially for pelvic and sacral GCTB, a catheter embolisation technique might be considered. Following identification of a dominant vessel or vascular plexus, minimally-invasive intervention could potentially interrupt tumour blood flow with intent to reduce size and improve symptoms.
3. Monitoring and surveillance: depending on tumour site and resource availability, the patient should enter a period of close MRI or radiographic surveillance with intent for earliest possible identification of any transformative tumour behaviour. A suggested surveillance interval of 6–8 weeks would be reasonable.
4. Supportive management: physical therapy, optimal pain control and safe symptom management strategies to improve or maintain quality of life.

Comprehensive GCTB management is tailored to each particular case, with consideration of symptoms plus maternal, fetal and tumour specific features - in particular the tumour site, size and growth behaviour. Optimal management in pregnancy requires specialist interdisciplinary management involving the radiologist, obstetrician, orthopaedic oncological surgeon and anaesthetist, with informed collaborative decision with the patient to determine treatment timing and implementation, surgical technique, and care for both mother and child.[4]

MRI surveillance during pregnancy introduces the issue of MRI safety. There has long been a theoretical risk of undergoing MRI in pregnancy, with the concern of teratogenesis from fetal exposure to intense electromagnetic fields. Follow-up studies of children scanned in utero however reported no harmful effects,[21–23] yet clear communication and informed consent should still be obtained. MRI follow-up would also be most appropriate for GCTB in the lumbosacral spine, pelvis and proximal femur given proximity to the fetus.

5. Conclusion

Pregnant and postpartum women with GCTB need individualised treatment with specialist involvement to ensure comprehensive understanding of the specific management requirements.

Although distribution of pregnancy-associated GCTB is similar to the general population, there was a strong association between progressive growth and aggressive tendency of GCTB during pregnancy and the postpartum period. As the exact mechanism of GCTB deterioration in pregnancy has not yet been convincingly identified, there is a need for a cautious and vigilant approach to peripartum GCTB workup, evaluation and surveillance.

Pregnancy itself has been implicated in aggressive GCTB growth and recurrence with hormonal influence thought to play a considerable role. There is a recognised pattern of disease progression, and we have provided significant findings supporting this hypothesis, with statistically significant growth in both primary and recurrent GCTB in both pregnant and postpartum patients through a period of extended surveillance.

Prospective identification of pregnant or recent postpartum patients at the time of GCTB diagnosis is necessary given the potential for accelerated growth and aggressive transformative behaviour of the tumour. This awareness should apply to risk of disease recurrence with recent or distant prior GCTB history, who might also require closer surveillance.

Future direction

Future research and practice change considerations include.

1. Routine assessment of ER and PR expression in biopsy/resection specimens for GCTB in pregnant and postpartum patients, especially those with observed disease progression;
2. Routine pregnancy testing (dipstick B-hCG) in female patients of reproductive age as part of workup for suspected primary GCTB and recurrent disease;
3. Accelerated pathway for diagnosis and management implementation, plus entering closer surveillance during pregnancy and postpartum period - with a reasonable surveillance interval between 6 and 8 weeks recommended;
4. Increased awareness, advice, engagement and surveillance for pregnant patients with recent or even distant history of prior GCTB for at least 12 months postpartum, with annual communication from the oncology service with opportunity for in-person or tele-appointment;
5. Identification of the exact physiological mechanism to explain the observed positive growth effects and behaviour change of GCTB associated with pregnancy.

Author contribution

1. Conception and design, or acquisition of data, or analysis and interpretation of data = 2Jeys L, 1Botchu R.

2. Design, or acquisition of data, or analysis and interpretation of data = 1Henderson RD, 1Jenko N, 2Jeys L, 1Botchu R.

3. Drafting the article or revising it critically for important intellectual content = 1Henderson RD, 1Shirodkar K, 1Hussein M, 1Jenko N, 2Jeys L, 1Botchu R.

4. Final approval of the version to be published = 1Henderson RD, 1Shirodkar K, 1Hussein M, 1Jenko N, 2Jeys L, 1Botchu R.

Funding

There is no funding source.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Chakarun CJ, Forrester DM, Gottsegen CJ, et al. Giant cell tumor of bone: review, mimics, and new developments in treatment. *Radiographics*. 2013 Jan;33(1):197–211.
2. Murphey MD, Nomikos GC, Flemming DJ, et al. Imaging of giant cell tumor and giant cell reparative granuloma of bone: radiologic-pathologic correlation. *Radiographics*. 2001 Sep;21(5):1283–1309.
3. Athanasou NA, Bansal M, Forsyth R et al. World health organization. WHO Classification of Tumours of Soft Tissue and Bone.
4. Vaishya R, Agarwal AK, Vijay V, et al. Metachronous multicentric giant cell tumour in a young woman. *Case Reports*. 2015 May 15;2015. bcr2015209368.
5. Formica VM, Bruno V, Di Uccio AS, et al. The giant cell tumor during pregnancy: a review of literature. *J Orthop Traumatol: Surgery & Research*. 2023 May 1;109(3), 103396.
6. Goldring SR, Schiller AL, Mankin HJ, et al. Characterization of cells from human giant cell tumors of bone. *Clin Orthop Relat Res*. 1986 Mar 1;204:59–75.
7. Komiya S, Zenmyo M, Inoue A. Bone tumors in the pelvis presenting growth during pregnancy. *Arch Orthop Trauma Surg*. 1999 Feb;119:22–29.

8. Ross AE, Bojescul JA, Kuklo TR. Giant cell tumor: a case report of recurrence during pregnancy. *Spine*. 2005 Jun 15;30(12):E332–E335.
9. Kathiresan AS, Johnson JN, Hood BJ, et al. Giant cell bone tumor of the thoracic spine presenting in late pregnancy. *Obstet Gynecol*. 2011 Aug 1;118(2 Part 2): 428–431.
10. Howard EL, Gregory J, Tsoi K, et al. Comorbidities and pregnancy do not affect local recurrence in patients with giant cell tumour of bone. *Cureus*. 2020 Jul 13;12(7).
11. Allouch S, Gupta I, Malik S, et al. Breast cancer during pregnancy: a marked propensity to triple-negative phenotype. *Front Oncol*. 2020;10, 580345.
12. Rockberg J, Bach BA, Amelio J, et al. Incidence trends in the diagnosis of giant cell tumour of bone in Sweden since 1958. *J Bone Joint Surg*. 2015 Nov 4;97(21): 1756–1766.
13. Donthineni R, Boriani L, Ofluoglu O, et al. Metastatic behaviour of giant cell tumour of the spine. *Int Orthop*. 2009 Apr;33:497–501.
14. Oursler MJ, Pederson L, Fitzpatrick LO, Riggs BL, Spelsberg T. Human giant cell tumors of the bone (osteoclastomas) are estrogen target cells. *Proc Natl Acad Sci USA*. 1994 Jun 7;91(12):5227–5231.
15. Murshed KA, Elsayed AM, Szabados L, Rashid S, Ammar A. Locally aggressive giant cell tumor of bone with pulmonary distant metastasis and extrapulmonary seeding in pregnancy. *JAAOS Global Research & Reviews*. 2020 Jan;4(1).
16. Taylor RM, Kashima TG, Knowles HJ, Athanasou NA. VEGF, FLT3 ligand, PlGF and HGF can substitute for M-CSF to induce human osteoclast formation: implications for giant cell tumour pathobiology. *Lab Invest*. 2012 Oct;92(10):1398–1406.
17. Barkin JL, Wisner KL. The role of maternal self-care in new motherhood. *Midwifery*. 2013 Sep 1;29(9):1050–1055.
18. Zhang R, Liu X, Huang W, et al. Clinicopathological features and prognosis of patients with pregnancy-associated breast cancer: a matched case control study. *Asia Pac J Clin Oncol*. 2021 Mar;17:396–402.
19. Yuan B, Han S, Yang S, et al. Radiologic an clinical changes after denosumab treatment for giant cell tumors of the mobile spine: a quantitative study. Insights into Imaging. 2022 May;13(1):93.
20. Dore RK. The RANKL pathway and denosumab. *Rheum Dis Clin*. 2011 Aug 1;37(3): 433–452.
21. Kanal E, Barkovich AJ, Bell C, et al. ACR guidance document on MR safe practices: 2013. *J Magn Reson Imag*. 2013 Mar;37(3):501–530.
22. McRobbie DW. Occupational exposure in MRI. *Br J Radiol*. 2012 Apr;85(102): 293–312.
23. Baker PN, Johnson IR, Harvey PR, et al. A three-year follow-up of children imaging in utero with echo-planar magnetic resonance. *Am J Obstet Gynecol*. 1994 Jan;170 (1):32–33.