CASE REPORT

Metachronous multicentric giant cell tumour in a young woman

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SUMMARY

Multicentric giant cell tumours (GCTs) are very rare and account for less than 1% of all GCTs of bone. We report a case of a young woman with metachronous multicentric GCTs with 5 documented lesions in the same lower limb. The initial lesion started during the first trimester of pregnancy around her right pelvis, which rapidly progressed as a painful swelling with gradually restricted mobility of her right hip joint. The radiological appearance of this tumour was that of a GCT and biopsy confirmed the diagnosis. The role of positron emission tomography (PET) has been highlighted to detect occult lesions. A possible hormonal correlation for these tumours has been discussed. The patient was managed successfully by an aggressive surgical approach for knee and talar lesions, whereas repeated embolisation and denosumab injections were given to treat her pelvic lesion.

BACKGROUND

Giant cell tumours (GCTs) are not uncommon bone tumours and account for about 4–5% of all tumours.¹ They usually present as an isolated lytic lesion involving the metaphyseal–epiphyseal region of a long bone in young patients. Less than 1% of these cases present as multicentric, either synchronous or metachronous, lesions.² So far, only about 100 cases of multicentric GCT (MCGCT) have been documented worldwide.³ Most of these cases were metachronous multicentric, but not always found in an ipsilateral limb. The diagnosis and treatment of metachronous multicentric GCTs (MMGCT) is a challenge. Recent advances in diagnosis such as fluorodeoxyglucose (FDG)-positron emission tomography (PET) have helped in finding aggressive and multifocal lesions. Treatment options include curettage (simple or extended) and en bloc resection; in inoperable cases, embolisation and medical treatment can be tried. We present a rare case of MMGCT in a young woman, first detected during her pregnancy, involving a mono-melic lower limb including right hemipelvis, proximal and distal femur, and patella and talus, and further discuss the diagnostic and treatment challenges faced in such a patient.

CASE PRESENTATION

A 20-year-old woman presented with progressive, painful swelling of right hip and pelvic region, which she first noticed during pregnancy 1½ years earlier. After delivery, she underwent biopsy from her right pelvic mass and was diagnosed as GCT of right iliac bone. The case was managed initially in

Iraq by curettage and bone cementing. After 6 months of pregnancy, a swelling started to reappear around the right pelvic region along with new swelling and pain on her right knee. At presentation to us, she had a hard, globular and tender 11×9×7 cm swelling around the right posterior gluteal region with glossy and stretched skin with engorged veins. The terminal movements of her right hip were restricted.

INVESTIGATIONS

Routine haematological and biochemical parameters were within normal range. Serum calcium, phosphorus, acid phosphatase, alkaline phosphatase and serum parathyroid hormone (PTH) were also normal. Radiological examination showed an expansile lesion at the margin of the previously cemented lesion in the right pelvic region ([figure 1](#)), with a large soft tissue component. There was destruction of cortices along with extension of tumour into the soft tissues around the right pelvic and hip region. However, the joint space was preserved. CT-guided fine-needle aspiration cytology was taken from the right iliac wing. Histopathological examination showed osteoclastic giant cells in sheets of stromal cells. The lesion was diagnosed as GCT of bone. Histopathological examination of the distal femoral, patellar and talar lesions further confirmed the cytological diagnosis of GCT ([figure 2](#)). The tumour cells did not show any evidence of malignancy. Radiological examination revealed lytic lesions at the

Figure 1 Anteroposterior radiograph of the pelvis showing a large osteolytic lesion involving the right side of the pelvis and proximal femur.

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Figure 2 Photomicrograph (×4 magnification) of the core biopsy of right distal femur, showing numerous multinucleated giant cells evenly distributed in sheets of stromal cells, suggestive of giant cell tumour.

right proximal femur, right distal femur and right patella (figure 3), with severe associated osteoporosis. A PET CT scan was made, which showed a large expansile FDG avid soft tissue mass lesion centred on the right iliac bone, showing multiple areas of necrosis, thickened internal septations and amorphous calcification. This lesion measured 14×15 cm at maximum in the axial plane (figure 4A). Another similar appearing FDG avid soft tissue lesion was seen involving the right patella, distal femur and talus (figure 4B, C). Later on, an X-ray of the ankle was taken to confirm the finding (figure 5) of an occult lesion of the talus. No malignant changes were noted in either lesion.

DIFFERENTIAL DIAGNOSIS

Various other neoplastic and non-neoplastic conditions can present themselves as MCGCTs, with the brown tumour of

Figure 3 Lateral radiograph of the right knee, showing osteolytic lesion with intralesional calcification in the distal femur and hidden patella with large soft tissue swelling.

hyperparathyroidism probably being the most common. This can be differentiated on clinical, radiological and histological grounds. Other multiple site neoplastic conditions that can imitate MCGCT are osteochondroma, enchondroma, multiple myeloma, metastases, adamantinoma, angiosarcoma, fibrous dysplasia, fibrosarcoma, osteosarcoma and multifocal infection. MCGCT can also occur in association with Paget's disease and pheochromocytoma.⁴

TREATMENT

The patient was given an injection of Denosumab (120 mg subcutaneously) in a stat dose, which was repeated after 3 and 6 months. Owing to invasiveness and the large size of the pelvic tumour, we decided to perform repeated selective embolisation of the pelvic tumour, as it was considered inoperable in its present stage. This highly vascular tumour was supplied blood by the branches of right internal iliac, external iliac and femoral arteries. Embolisation was performed with gelfoam slurry and pledgets. Four sittings of embolisation were performed at 3-week intervals. These resulted in significant reduction in pain score (1/10) and swelling of this lesion. Right patellectomy with repair of quadriceps and patellar tendon was carried out for the patellar lesion. The involved patella was eggshell-like in consistency and had ballooned out due to the expansile nature of the lesion, but its articular surface was found intact at surgery. The patient also underwent curettage and cementing of the distal femoral lesion with prophylactic distal femoral locked plate fixation (figure 6). Curettage and autologous bone grafting was performed for the talar lesion.

OUTCOME AND FOLLOW-UP

After 6 months of follow-up with repeated embolisation, the pelvic lesion started showing improvement and signs of calcification could be well appreciated on X-rays (figure 7). At 1-year follow-up, all the lesions were pain free and the patient could manage her activities of daily living with little assistance. She was not keen for any operative procedure for her right pelvic tumour.

DISCUSSION

Of all primary bone neoplasms, GCTs account for up to 4–5% of cases.¹ MCGCTs are even rarer and represent only 1% or less of all GCTs.² The age group affected by MCGCTs is reported to be younger than that of solitary GCTs.^{2–3} Females again outnumber males, as they do in solitary GCT.^{2–3} This raises a possibility of these tumours having some hormonal relationship, since our young female patient also started having these metachronous lesions during her pregnancy and immediately in postpregnancy period. It is proposed that human osteoclasts are the target cells for oestrogen hormone and the hormone inhibits bone resorption by osteoclasts.⁵ This may explain the onset of this tumour in our patient during pregnancy, where there is relative deficiency of oestrogen hormone as compared with progesterone.⁶

The postulated pathogeneses of multicentricity are reported to be due to contiguous extension, tumour cell seeding while treating initial lesion, malignant transformation, benign metastasis and de novo formation.³ Dhillon and Prasad³ reported that MCGCTs commonly involve the short bones and is more common in the metadiaphyseal region of long bones. Hoch *et al*² classified GCT tumours as synchronous (developing simultaneously or within 6 months from the onset of initial lesion) or metachronous (subsequent tumour(s) appearing 6 months after the diagnosis of the first lesion). We classified our case as metachronous, because all the tumours occurred after 6 months of

Figure 4 (A) Positron emission tomography (PET) CT scan image of the right hip showing a large pelvic tumour with increased uptake of fluorodeoxyglucose (FDG). (B) PET CT scan image of the right knee showing increased uptake of FDG. (C) PET CT scan image of the right ankle showing increased uptake of FDG.

the onset of the first tumour. Synchronous MCGTs are reported to be far less in incidence compared to metachronous tumours, however, their exact incidence, the reasons for this discrepancy and the difference in their prognosis are not known.

Cases of MCGCT are usually reported to have less than three lesions but in one patient as many as 10 tumours have been reported.⁷ Our patient also had five lesions involving only one lower limb. The reason for such monomelic involvement and metachronous nature is difficult to explain.

Various other neoplastic and non-neoplastic conditions can present themselves as MCGTs, with the brown tumour of hyperparathyroidism probably being the most common. This can be differentiated on clinical, radiological and histological grounds. Other multiple site neoplastic conditions that can imitate MCGTs are osteochondroma, enchondroma, multiple myeloma, metastases, adamantinoma, angiosarcoma, fibrous dysplasia, fibrosarcoma, osteosarcoma and multifocal infection.

MCGTs can also occur in association with Paget's disease and pheochromocytoma.⁴ Since brown tumours closely mimic GCTs clinically as well as pathologically, a metabolic and radiological work up should be carried out when multifocal GCT is suspected, and PTH, especially, must be checked.⁸ Metabolic work up was within normal range in our patient. Local recurrence in GCT is usually noticed in the first 2–3 years after the initiation of treatment.⁹ Multifocal lesions are not uncommon in GCTs,

Figure 5 Lateral radiograph of the right ankle showing a large lytic lesion in the talus.

Figure 6 Anteroposterior radiograph of the right knee showing bone cementation in distal femur and locking plate fixation.

Figure 7 Follow-up radiograph of the pelvis showing diffuse calcification of the pelvic tumour.

and a PET scan is especially a useful investigation tool to diagnose such lesions.¹⁰ Multifocal lesions are usually more aggressive locally than solitary ones and hence may have higher rates of recurrence, as in our case, where there was recurrence of the pelvic lesion even after curettage and cementing.

Management of GCT can be challenging. When possible, en bloc resection is the most successful surgical technique for treating multicentric and solitary lesions.¹¹ Intralesional curettage has also been used for management of these lesions but may be associated with high recurrence rates, sometimes as high as 20%, without the use of adjuvants.⁹ The recurrence rates can be further brought down with the use of local adjuvants such as phenol, bone cement, etc, or by performing extended curettage using a high-speed burr.⁹

However, if the tumour seems inoperable due to its large size, increased vascularity, etc, repeated embolisation of the tumour and injections of Denosumab provide resolution and shrinkage of the tumour.¹² Denosumab is a human monoclonal antibody that binds to RANKL (receptor activator of nuclear factor κ B ligand), a protein that is involved in osteoclastic function and formation. It is indicated in patients with bone metastases for prevention of skeletal-related events. The hallmark of GCT is the presence of numerous multinucleated osteoclast-type giant cells and since these cells are known to express RANKL, they are responsible for the aggressive osteolytic nature of the tumour. No available treatment option is reported to be effective in curing this disease, especially in surgically unsalvageable cases.⁴ Several studies have shown the superiority of Denosumab over bisphosphonates in reducing the skeletal morbidity arising from tumours and delaying bone metastasis.

Transarterial selective embolisation is a safe and effective interventional treatment for pain relief and devascularisation of primary and metastatic bone tumours such as GCT.¹³ Selective embolisation can make inoperable lesions (as in our case) viable for surgical treatment, after tumour shrinkage. Embolisation may help devascularise the tumour, reduce the size, calcify it and provide pain relief. It can act as a palliative or as adjunctive therapy for such a highly vascular bone tumour. We are not sure about the degree of contribution by Denosumab and embolisation individually, but believe that both have had an additive effect on the tumour shrinkage and clinical improvement of the pelvic lesion. Denosumab might have also helped in healing of the other satellite lesions.

Awareness about this rare entity is important to reach early diagnosis by excluding other mimicking lesions. If GCTs are

located in more than one site, then a rigorous search for yet other hidden or evolving lesions must be made. The treatment modalities of MCGCTs include Denosumab injection and surgical excision of the tumour. In inoperable tumours, selective repeated embolisation can help as a palliative or adjunct therapy and may make such tumours amenable to surgical resection.

Patient's perspective

I am delighted to have treatment here in India for a problem which was thought to be untreatable in my own country. I was bedridden before having this treatment, but now I can walk and am pain free.

Learning points

- ▶ Multicentric giant cell tumours of the bone are rare entities and usually affect younger females.
- ▶ Multiple bone involvement can occur simultaneously (synchronous) or at different times (metachronous).
- ▶ Denosumab and selective embolisation of the tumour are useful for palliative treatment of inoperable tumours.
- ▶ A positron emission tomography scan is an effective investigation tool for the diagnosis and for evaluating these tumours.

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