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CASE REPORT

Multicentric Giant Cell Tumor of Bone: Metachronous Presentation—a Case Report

Nur Asma Sapiai[1,5] · W. S. Wan Fatihah[2,5] · W. I. Faisham[3,5] · M. Z. Anani Aila[4,5]

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Abstract

Giant cell tumors (GCT) of bone are a benign aggressive tumor with features of frequent local recurrence. It has the potential for metastasis and malignant transformation. GCT of bone represents about 4–9.5% of primary bone tumors. Metachronous GCT happen in less than 1% while metastatic spread in these lesions is very uncommon. Furthermore, reports of multicentric metachronous GCT are very rare in literature. We present a case of a 35-year-old male patient, who suffered from multicentric metachronous GCT, which involved the radius, humerus, femur, and pelvic with pulmonary metastasis. Local control by multiple resections of the tumor and chemotherapy for pulmonary metastases was able to control the disease with long-term survival and good functional outcome. These tumors had a typical radiological appearance and the diagnosis was confirmed on histopathology. Long follow-up needed in this case in view the illness occurs for long period.

Keywords Bone tumor · Multicentric metachronous giant cell tumors · Pulmonary metastasis

Introduction

Giant cell tumors (GCT) of bone occur for about 4 to 9.5% of all primary bone tumors. Multicentricity of GCT of bone is an extreme rarity that accounts for less than 1% of these tumors [1–3]. The biological behavior and the presentation seem to be different from solitary lesions. Most of the multicentric giant cell tumors are synchronous. It is occurring within a poorly defined time of the initial tumor [2]. In this paper, we present the case of a multicentric metachronous giant cell tumor as well as a review of the literature on this tumor. The typical features of multicentricity are also pointed out.

Case

A 35-year-old gentleman, ex-smoker, first presented to the hospital in 1998 at the age of 19 years old with a complaint of progressively swelling and redness of right knee after a fall during playing football. CT scan showed an aggressive bone lesion involving the distal right femur extending into the knee joint and biopsy confirmed a giant cell tumor of the bone. He then underwent right above knee amputation due to massive soft tissue and vessel involvement.

He presented again 7 years later with a pathological fracture of the right distal radius which histopathological reported as a giant cell tumor suggestive of metachronous. MRI of the right wrist (Fig. 1) showed an aggressive bone tumor of the distal right radius with a local extension including the wrist joint and carpal bone. CT thorax was also done and showed metastasis lung nodule. He underwent wide resection and allograft with wrist fusion, while thoracoscopic resection was done for lung nodule. In view of progression metastatic nodules, he had chemotherapy regimen consisted of VAC (cyclophosphamide 500 mg/m^2 IV bolus day 1, Adriamycin 50 mg/m2 IV bolus day 1, vincristine 2 mg (max) iv bolus day 1, repeat

✉ Nur Asma Sapiai
drnurasma@usm.my; asmahannif@gmail.com

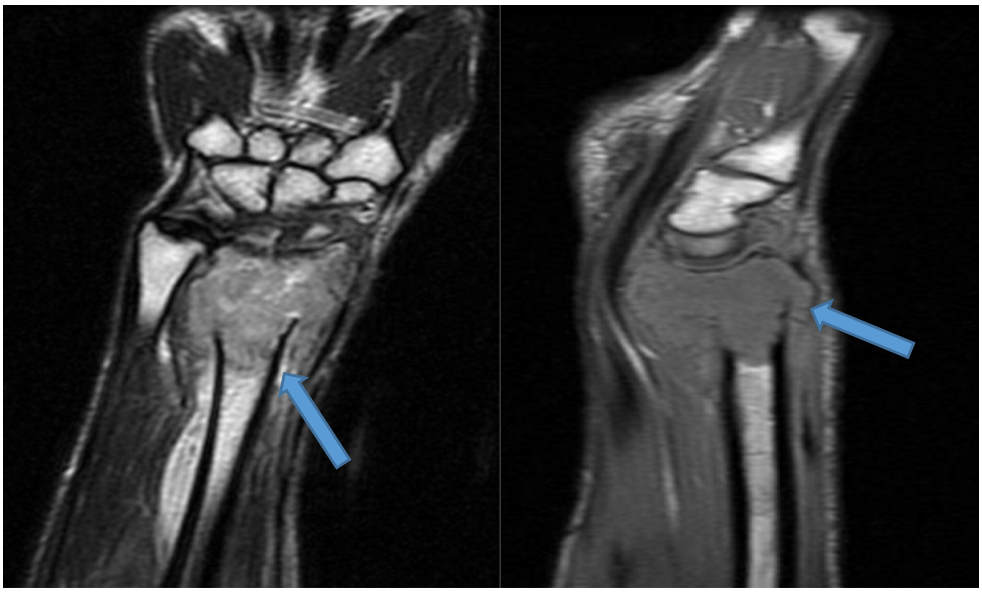
1 Department of Radiology, School of Medical Sciences, Universiti Sains Malaysia, Health Campus, 16150 Kota Bharu, Kelantan, Malaysia

2 Department of Nuclear Medicine, Radiotherapy and Oncology, School of Medical Sciences, Universiti Sains Malaysia, Health Campus, 16150 Kota Bharu, Kelantan, Malaysia

3 Department of Orthopaedic, Orthopaedic Oncology Reconstructive Surgery Unit, School of Medical Sciences, Universiti Sains Malaysia, Health Campus, 16150 Kota Bharu, Kelantan, Malaysia

4 Department of Pathology, School of Medical Sciences, Universiti Sains Malaysia, Health Campus, 16150 Kota Bharu, Kelantan, Malaysia

5 Hospital Universiti Sains Malaysia, Health Campus, 16150 Kota Bharu, Kelantan, Malaysia



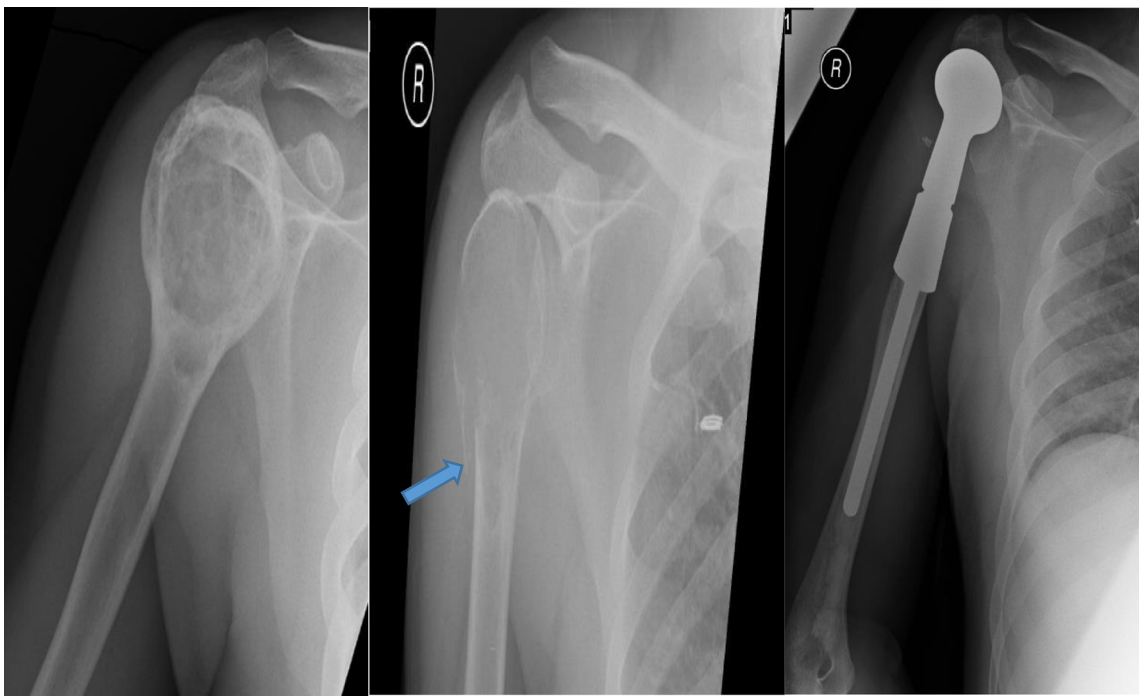
(a) (b)

Fig. 1 (**a**) Coronal and (**b**) sagittal MRI of wrist showing a massive infiltration of the bone with destruction of the cortex (arrow)

every 3 weeks for target of 6 cycle). The allograft reconstruction complicated with fracture and stabilized with deformity 2 years later.

He presented again 12 years after the initial presentation with right shoulder pain following a fall in the bathroom. Radiograph of the proximal right humerus (Fig. 2) showed well-defined lytic lesion with a narrow zone of transition involving the head and neck of the right humerus up to the articular surface. It is associated with a fracture of the neck of the right humerus. The core biopsy showed reactive changes, benign fibrous histiocytosis, but unable to rule out giant cell tumor.

In 1 month apart, he complains of right buttock pain, especially on movement. The pelvic radiograph (Fig. 3) reveals an



(a) (b) (c)

Fig. 2 Radiograph of right proximal in AP (**a**) lytic lesion of the proximal humerus, (**b**) presenting with pathological fracture (arrow). **c** The lesion was done wide resection and endoprosthesis of right humerus

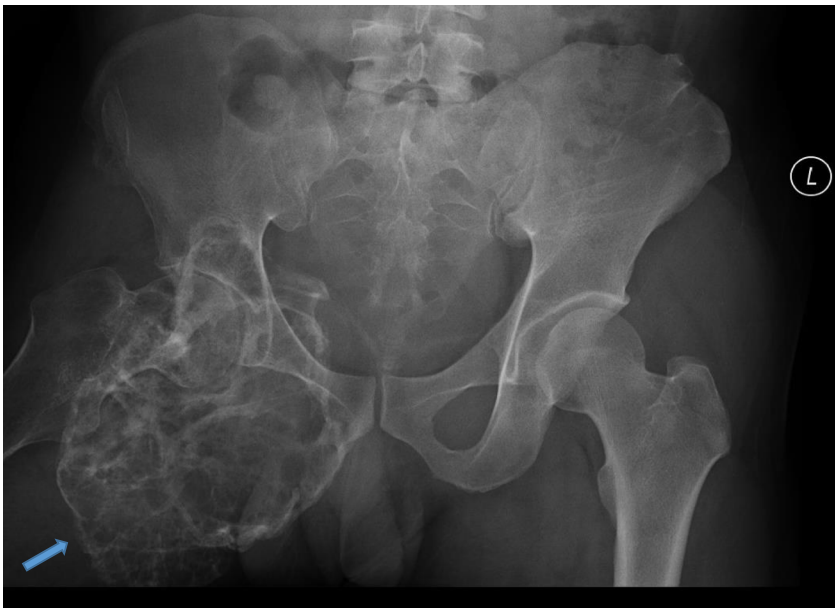


Fig. 3 Radiograph of pelvis in AP reveals an expansile lytic lesion (arrow) involving right ischium and inferior pubic rami

expansile lytic lesion involving the right ischium and inferior pubic rami. CT scan of the pelvis (Fig. 4) showed a large expansile osteolytic lesion with soft tissue component within seen primarily at the right ischium with extension into the right inferior pubic rami and right iliac bone. Sclerosis of the lesion margin with a narrow transitional zone. There is also an osteolytic lesion seen in the remaining right femur and sacral bone. A bone scan in 2012 showed increase tracer accumulation at the right shoulder and right femoral with photon-deficient area is seen at the right ischium. These are suggestive of metachronous GCT lesion of these sites. He was initially treated by local radiotherapy; however, expansile lesion prevents proper sitting and interferes with his activity particularly riding a motorbike. He underwent right limited hemipelvectomy due to disability of above knee amputation (AKA) in 2014.

Another bone scan was done in 2014 (Fig. 5), scan findings consistent with a giant cell tumor of the right head of the humerus and distal end of the right radius. Uptake at the right ilium (along the surgical margin) is likely due to inflammatory post-surgical changes. Right proximal humerus resection and endoprosthesis replacement were done a year later due to persistent pain and progressive radiological changes over a short period. All histopathological evaluation of the lesions showed a typical giant cell tumor of the bone suggestive of a multicentric metachronous giant cell tumor without malignant changes (Fig. 6). Immunohistology evaluation of Ki67, P53, and RANKL showed strong positivity for all the samples taken. Currently, the patient is stable, with no new complaint with stable lung metastasis.

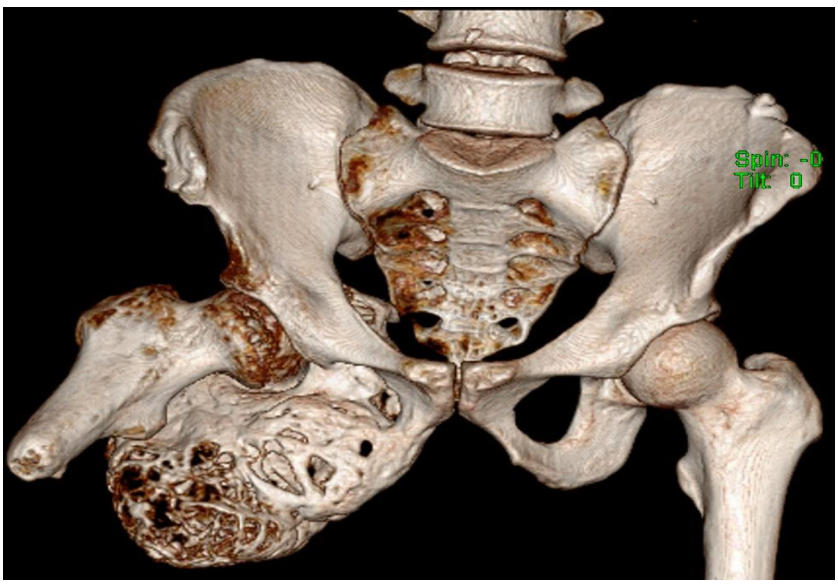
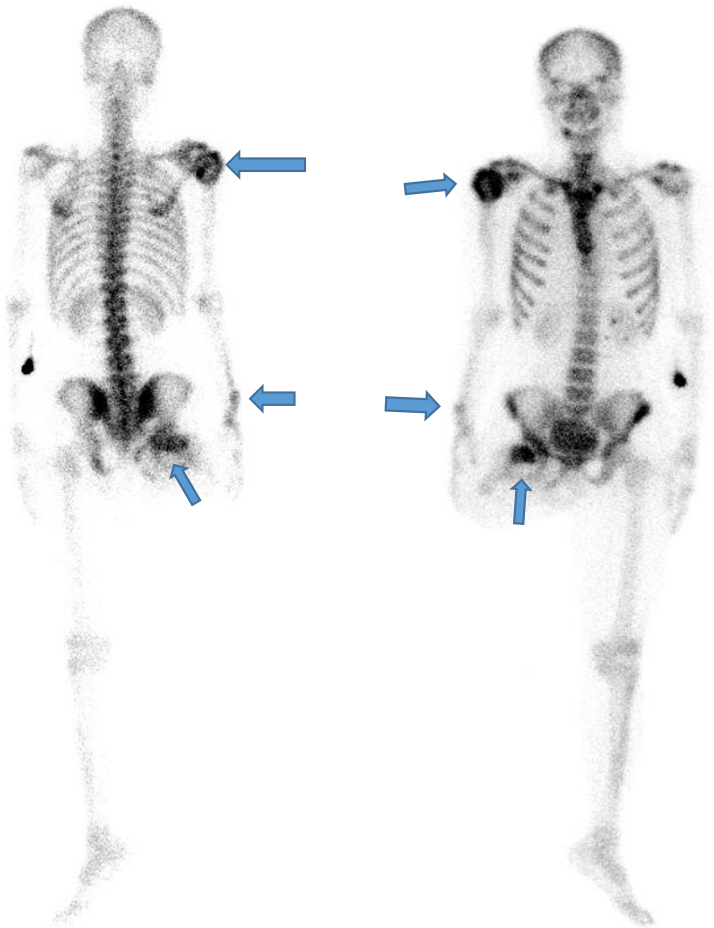
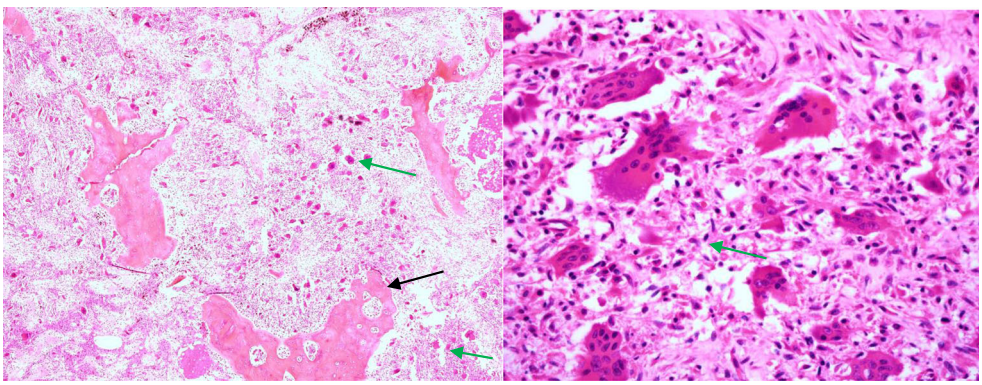


Fig. 4 3D CT reconstruction showed aggressive bone lesion involving right ischium and inferior pubic rami



(a) (b)

Fig. 5 **a** and **b** Skeletal scintigram showed increase tracer uptake at right head of humerus and distal end of right radius. Tracer uptake at the right ilium likely due to inflammatory post-surgical changes



(a) (b)

Fig. 6 Right hemipelvis tumor and right above knee amputation stump pathology show (**a**). The tumor is composed of diffusely arranged stromal cells with many scattered osteoclast-type multinucleated giant cells (green arrow). The cortical bone (black arrow) is eroded by the tumor (H&E ×40). **b** The stromal cells (green arrow) are spindly, having hyperchromatic nuclei with moderate cytoplasm. Scattered osteoclast-type multinucleated giant cells are also present (H&E ×400)

Discussion

Giant cell tumor (GCT) of bone is a benign primary neoplasm accounting for 4 to 9.5% of all primary bone tumors [1–3]. It typically presents as a solitary lytic lesion in patients between the ages of 20 and 50 years, the peak prevalence in the third decade of life [2]. The metaphyseal-epiphyseal region of a long bone is the commonest site in adults. Almost half of the cases happen adjacent to the knee joint [1]. It is followed by the proximal part of the humerus and distal part of the radius [3]. Comparing with solitary lesions, multicentric GCT more frequently occur in the short bones of the hands and feet. Furthermore, it is more frequently restricted to the metaphyseal or diaphyseal-metaphyseal region of the long bones [4].

Multicentric GCT of bone is rare and accounts for less than 1% of GCT [1, 5]. Multicentric lesions are believed to occur more in younger patients with the presentation at the average age of 20 years [1]. It occurs more often in females (twice as often as in males) and skeletally immature patients [3].

The presenting symptoms are usually pain, local swelling, or palpable mass. In some rare cases, the tumor was discovered by incidental radiological imaging without complaining of symptoms [6].

Multicentric GCT of bone is classified into two as either metachronous or synchronous. Synchronous referred to when multiple tumors are discovered at the initial presentation or when a second lesion is diagnosed within 6 months. Synchronous tumors occur more frequently compared to metachronous tumors [2]. While for metachronous, the second tumor develops more than 6 months after the first lesion [1, 3]. In most cases of these groups, additional tumors are developed within 2 years after the discovery of the primary lesion, but they also may develop up to twenty or more years later.

To date, the pathogenesis of the multicentricity in GCT is still unclear. There are multiple possible mechanisms including contiguous spread, iatrogenic seeding of tumor cells, benign metastasis, malignant transformation, and de novo multifocal formation [2, 4]. Solitary benign GCT can metastasize to lung or undergo malignant transformation. Pathologic examination of multicentric GCT shows findings similar to histologically benign solitary tumors. This suggests that the multifocality of some GCT is not a metastatic phenomenon but favor of the separate development of the tumor at multiple sites [5].

Diagnosis of multicentric GCT is based on clinical, serological, and radiographic findings. They must be distinguished from other multifocal lesions, such as brown tumors of hyperparathyroidism, fibrous dysplasia, and multiple myeloma [4].

The plain radiographic film usually reveals an expansile, eccentric radiolucent lesion at the epiphyseal, subchondral region with well-defined geographical margins [1]. It usually has a narrow zone of transition. However, a broader zone of transition is seen in more aggressive GCT. No surrounding sclerosis (80–85%) or internal matrix calcification/mineralization was found [4]. The overlying cortex is usually thinned, expanded, or deficient. The periosteal reaction is also in about 10–30% of cases. The soft tissue mass is not infrequent in this disease. The pathological fracture may also be present. Some suggested that GCT of short bones are more likely to have a more aggressive course (17%) in multicentric GCT compared to 2% in solitary GCT. A skeletal survey for these tumors as well as multiple follow-ups is recommended to detect metachronous GCT.

MRI is preferred imaging for good tumor delineation, extraosseous, and articular surface involvement. The tumor is isointense in T1 imaging and slightly hyperintense in the T2 imaging with enhancement post-contrast. It also can have necrotic areas within [7].

CT is an alternative method of investigation, especially to reveal the integrity of the cortex, delineate the intra-osseous extension of the tumor, and also metastasis [7]. The risk of pulmonary metastases is higher in multicentric GCT which is reported about 5–10% in patients with multicentric GCT and at 1–2% in patients with solitary GCT [8].

Scintigraphic bone scan commonly demonstrates a diffuse-increased radionuclide uptake or a peripherally increased uptake with photogenic centrally giving the appearance of "donut" sign [4]. Angiography usually was performed in the setting of preoperative embolization. About two-thirds of cases show hypervascular tumors while the rest being hypovascular or avascular [7].

The histopathological examination of the tumor is very variable and consists mainly of giant cells containing multiple nuclei and also single nucleus stroma cells, histologically not distinguishable between multicentric GCT from the solitary lesion. However, fibroblastic and fibrohistiocytic areas are considered to be a major component of this type [2].

The goal of the treatment of this tumor is to eradicate the lesions and to preserve the function of the affected bones and joints [6]. The preferred treatment method is intralesional curetting [8] and filling the cavity with bone cement. Thermal cauterization of the bone cement may help destroy microscopic tumor cells and reduce recurrence. Recurrence after intralesional curettage is about 25% and wide excision is associated with a rate of 5%. However, wide excisions usually require endoprosthetic replacement or arthrodesis because of the tumors' frequent juxta-articular localization. Therefore, it has greater morbidity [1].

Exclusive radiation therapy is generally ineffective in these tumors; however, it is the choice of treatment for lesions that are not suitable for surgical removal [8]. After treatment with curettage and bone cement, additional radiation therapy is suggested in patients with soft tissue involvement because they have an increased risk of local recurrence.

Malignant transformation of GCT of bone can be defined as a sarcoma, usually a fibrosarcoma or osteosarcoma.

Approximately, about 5% of solitary lesions undergo malignant changes. Meanwhile, there is no data regarding the malignant transformation of multicentric lesions.

Metachronous giant cell tumors can occur for long period as in this case. Therefore, patients need longer and regular follow-up to evaluate the symptoms. Immediate radiograph and further imaging are needed once suspicious. Treatment of giant cell tumor with pulmonary metastasis is still controversial and the course of metastatic pulmonary disease progression is unpredictable. The small nodule had been shown to regress spontaneously after primary control of the disease. Various modalities of treatments include surgical resection of accessible pulmonary metastases that have shown a good option to prevent progression. Multiple lesions were treated with chemotherapy regimens and interferon α-2β with variable success to prevent pulmonary dysfunction. Radiation therapy was an option to control the pulmonary progression but no long-term outcome on the success of the treatment [9].

Bones scan screening at unusual sites such as at the diaphyseal region and small bones is recommended at least once. Multicentricity has to be taken into consideration when the patients are younger or when the lesion is located at unusual sites such as the diaphyseal region and small bones of the hands or feet.

Conclusion

In summary, a metachronous giant cell tumor is rare. It tends to occur in younger patients. Therefore, a careful history and physical should be performed on all younger patients presenting with GCT to look for additional sites of the lesion. As in our case, this patient had a multicentric metachronous giant cell tumor that required multiple surgeries for local control.

Therefore, any symptomatic bone lesion needs further radiological evaluation because of the possibility of a multicentric lesion. Meanwhile, multiple lesions need regular follow-up based on clinical and further radiological imaging. Local control of the disease is the main aim. Besides that, control of pulmonary metastases is also important to prevent progression and early mortality.

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Author Contribution All the authors contribute in this case report.

Declarations

Conflict of Interest The authors declare no competing interests.

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