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CASUISTIC PAPER

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Primary leiomyosarcoma of bones – a rare entity in two different presentations

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ABSTRACT

Introduction. Leiomyosarcomas (LMS) originate from smooth muscle cells. They are very rare malignant neoplasms. Bony Leiomyosarcoma is a variant of spindle cell sarcoma, primarily affecting long bones, predominantly the distal femur and the proximal tibia followed by craniofacial skeleton.

Aim. To describe clinical presentation and diagnostic approach of primary leiomyosarcoma of bones in two different patients.

Description of the cases.

Case 1. A 64-year-old male with a fracture of left distal femur after a fall was investigated and found to have a pathological fracture. An open biopsy of the fracture site confirms leiomyosarcoma.

Case 2. A 58-year-old previously healthy female presented with a swelling on right side mandibular region. Orthopantomogram radiograph (OPG) of mandible and Cone beam CT (CBCT) mandible was taken initially and revealed a large area of bone destruction of the right side of the mandible associated with a soft tissue mass. Initial incisional biopsy made the diagnosis of spindle cell sarcoma followed by excisional biopsy, which confirms the diagnosis of moderately differentiated leiomyosarcoma.

Conclusion. Primary leiomyosarcoma of bones is very rare. Imaging features are helpful in the evaluation of such conditions, but final diagnosis should be based on histopathologic and immunohistochemical features.

Keyword. bones, leiomyosarcoma, malignant neoplasms

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Introduction

Primary malignant bone tumours are rare. Majority (>90%) of them are osteosarcomas, Ewing sarcomas and chondrosarcomas. Clinical presentations, diagnostic approaches and treatment options of these tumours are well established. There are other rare primary malignant bone sarcomas (RPMBS) that are even rarer with lack of specific clinical and radiological characteristics. RPMBS comprise of wide variety of tumours showing complex histopathological features requiring ancillary studies such as immunohistochemistry and molecular genetic studies to arrive at a definitive diagnosis. Therefore, specific diagnosis of such a RPMBS is a challenging task for clinicians.[1,2] Although it is rare, awareness of this condition may help clinicians to consider in their differential diagnoses list, when a patient with a bone tumour presenting with non-specific clinical and radiological features.

Histopathologically, RPMBS show differentiation towards variety of cell types giving rise to architectural patterns which can be used to narrow down differential diagnoses. Those entities include sarcomas comprising spindle cells, round cells and vascular spaces lined by endothelial cells. Some of those are biphasic in nature.[1]

Primary intraosseous leiomyosarcoma is a malignant neoplasm showing smooth muscle differentiation without the production of osteoid. They primarily affect long bones, predominantly the distal femur and the proximal tibia. The second most common site affected is the craniofacial skeleton.[3] Spinal involvement is another reported site.[4]

In the initial periods these tumours grow slowly without characteristic clinical features. Most frequent clinical symptom is pain. Sometimes, pathological fractures can be seen.[4] However oral/maxillofacial involvement of lesions may manifest in the form of a significantly malignant tumour with rapid growth, needing radical surgical management and adjuvant radiotherapy.[5]

Aim

Here we present two cases of primary leiomyosarcoma of the bone, affecting the femur in a male patient and the mandible in a female patient.

Description of the cases

Case 1.

A previously healthy,64-year-old male presented to an orthopaedic unit at the National Hospital of Sri Lanka, with a fracture of left distal femur after a fall on the floor (Fig. 1).

He had intermittent pain in left thigh, which exacerbated at night in preceding 2 months of the fracture. Previously he never had trauma or radiation therapy to that site. There were no symptoms pointing towards a systemic pathology such as recent loss of appetite or loss of weight. Family history was insignificant.

Fig. 1. Initial X ray of left distal femur

On examination the fracture site was swollen and tender. Distal neurovascular status was normal. Abdominal and per rectal examination as well as other systemic examinations did not reveal any significant findings.

Diagnosis of a pathological fracture was made considering the age, site and low energy that caused the fracture and investigation were carried out. His blood investigations results are summarized in Table 1.

Table 1. Summary of biochemical results of case 1

Investigation	Results
White blood cells	7.3×10^9/l Neutrophils – 63%, Lymphocytes – 15%, Eosinophils – 14%
Erythrocyte sedimentation rate (ESR)	70 mm/1hr
C-reactive protein (CRP)	73 mg/l
Liver function tests	AST – 34 U/l, ALT – 21 U/l, Total bilirubin – 1.1mg/dl
Serum Creatinine	1.0 mg/dl
Serum Electrolytes	Na^+ – 140 mmol/l, K^+ – 4.1mmol/l, Cl^- – 100 mmol/l
Serum calcium	8.8 mg/dL
Thyroid stimulating hormone (TSH)	1.43 mU/l
Prostate specific antigen (PSA)	0.89 ng/ml

Patient underwent MRI scan of the affected femur, which revealed heterogeneously low signal intensity lesion in T1W and T2W images with heterogeneous post contrast enhancement (Fig. 2-5).

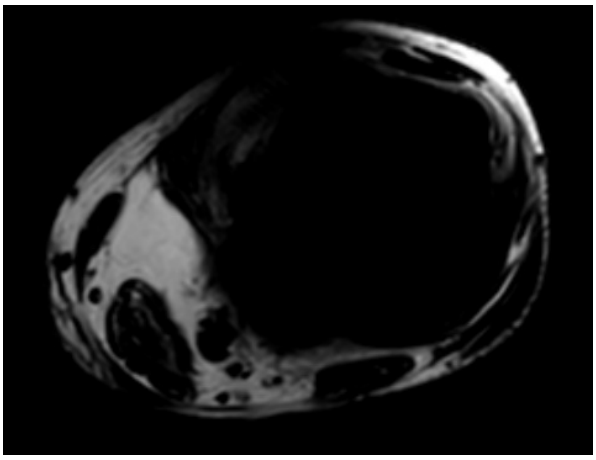

Fig. 2. MRI-T1W axial image

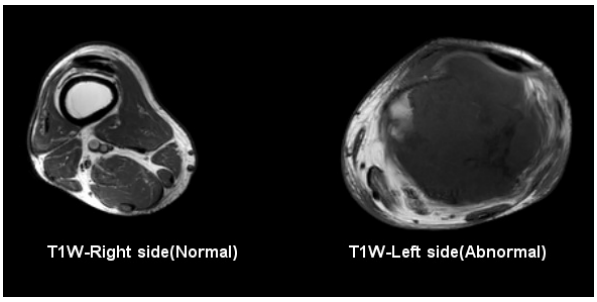

Fig. 3. MRI- T1W axial image

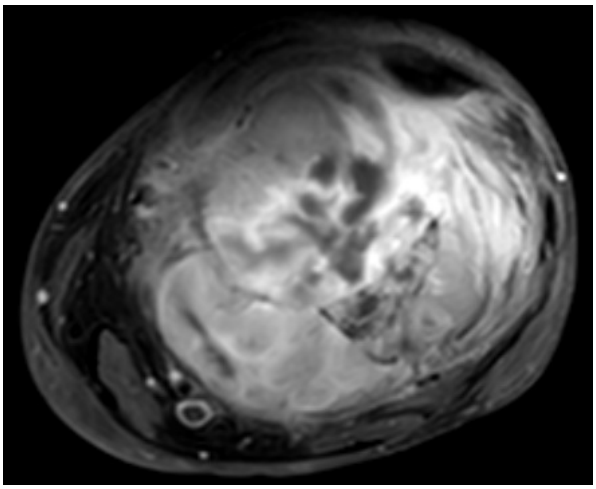

Fig. 4. MRI-Post contrast T1W axal

An open biopsy was taken from the fracture site and skeletal traction was applied using a Steinmann pin through the proximal tibia as the initial management.

Histopathological examination of the biopsy sample revealed malignant spindle cell tumour composed of long intersecting fascicles. The tumour cells showed highly pleomorphic, vesicular nuclei with blunt ends and small nucleoli. The cytoplasm was eosinophilic and abundant. Scattered multinucleate giant cells were also noted. The mitotic activity was brisk (12 per 10 high power fields) with abnormal forms. Areas of myxoid stroma and foci of necrosis were evident. There were no malignant osteoid or chondroid areas within the examined specimen. Numerous thin-walled capillaries, nuclear hyperchromasia and diffuse infiltration of skeletal muscle fibers are not seen.

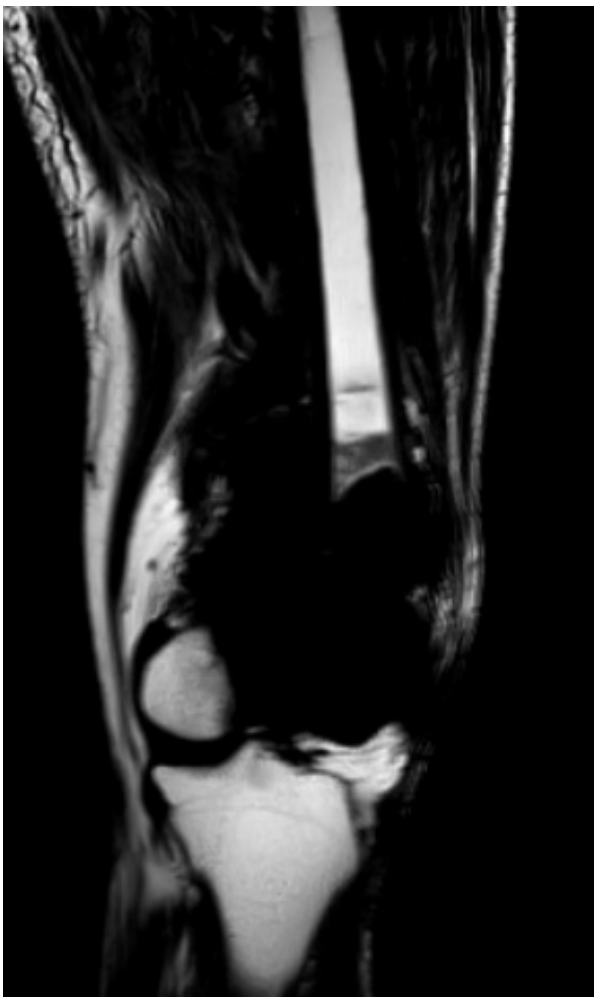

Fig. 5. MRI-T2W m DIXON coronal image

Immunohistochemical (IHC) assay showed diffuse and strong cytoplasmic positivity of tumour cells to smooth muscle actin (SMA). IHC for desmin, S-100, CD31, MyoD1, AE1/AE3 and CD117 were negative. Although two smooth muscle cell markers are required for a definitive diagnosis of a leiomyosarcoma, facilities to perform IHC for additional, novel smooth muscle markers such as h-caldesmon are not available in our institution. Therefore, based on the histomorphology which is highly characteristic of a leiomyosarcoma and on the strong and diffuse cytoplasmic positivity for SMA, a diagnosis of a leiomyosarcoma was made. It has been reported in the literature that loss of one or more markers of myogenic differentiation can be observed in leiomyosarcomas when they acquire poorly differentiated areas. It also mentioned that such loss may have an impact on the prognosis as well.[6]

When considering the differential diagnoses, features suggestive of a low grade myofibroblastic sarcoma such as numerous thin-walled capillaries, nuclear hyperchromasia and diffuse infiltration of skeletal muscle fibres were not seen in the biopsy specimen. The spindle cells in a fibroblastic osteosarcoma are arranged in a storiform pattern rather than a fascicular pattern and usually contain (at least focally) malignant osteoid. In addition, the age and the immunohistochemistry profile do not keep in with the diagnosis of an osteosarcoma. Therefore, the histomorphology and immunohistochemistry findings were used in the diagnosis of leiomyosarcoma.

After a multidisciplinary team discussion, the patient was transferred for specific oncology unit for chemotherapy. Traction with the Steinmann pin was continued.

Case 2.

A 58-year-old female presented to oral and maxillofacial unit at the National Dental Hospital (Teaching), complaining of a gradually increasing lump on the right mandibular region of the face for last two months. However, the patient did not have significant pain in the region except for mild difficulty in opening of the mouth. She denied numbness in the region or in the lower lip as well as otalgia.

On examination, a significantly large swelling (8cm x 6cm) was noted in the right mandibular region which involves angle and the ramus of the mandible. It was a well circumscribed hard swelling with clear margins, with no surface changes, skin tethering or discharging fluids and was deeply fixed but was not tender. There were enlarged level II lymph nodes on the right side.

Table 2. Summary of biochemical results of case 2

Investigation	Results
White blood cells	6.2×10^9/l Neutrophils – 70%, Lymphocytes – 25%, Eosinophils – 3%
Erythrocyte sedimentation rate (ESR)	52 mm/1hr
C-reactive protein (CRP)	45 mg/l
Liver function tests	AST – 28 U/l, ALT – 25 U/l, Total bilirubin – 1.0mg/dl
Serum creatinine	0.97 mg/dl
Serum electrolytes	Na^+ – 138 mmol/l, K^+ – 4.0mmol/l, Cl^- – 101mmol/l

There were no restrictions to shoulder movements. Maximum mouth opening measured between central incisors was 30mm.

Intra oral examination revealed poor oral hygiene with multiple carious teeth. The right-side lower quadrant was partially edentulous, which she had undergone extractions long time ago.

There was no significant lingual expansion of right-side mandible and there was no taste disturbance or altered sensation in right side of the tongue.

The lesion was not extending posteriorly beyond the anterior pillar fauces or towards the maxillary tuberosity along the pterygo-mandibular raphe area.

Her blood investigations results are summarized in table 2.

A orthopantomogram radiograph (OPG) and cone beam CT (CBCT) of the mandible was performed initially. The OPG image revealed a large area of bone destruction of the right side of the mandible involving the coronoid and condylar processes and proximal most part of the angle of the mandible (Fig. 6). The CT scan of the mandible demonstrated a soft tissue density enhancing lesion in relation to the bone destruction (Fig. 7, 8).

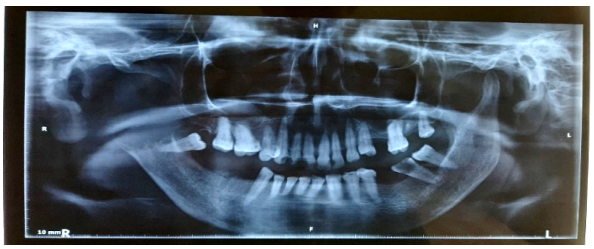

Fig. 6. OPG image

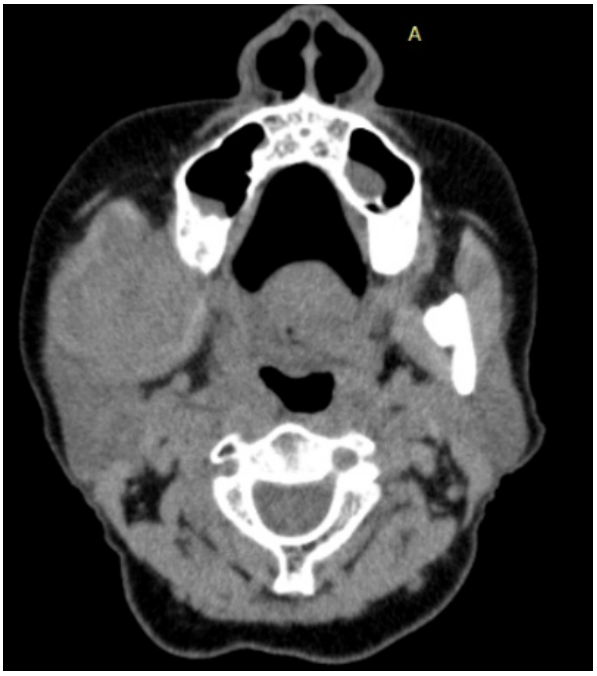

Fig. 7. CT axial image-Soft tissue window

Clinically, differential diagnoses were bone sarcoma or an odontogenic malignant tumor. With the provi-

sional clinical diagnosis of a malignancy, an incisional biopsy was performed under general anesthesia. The histopathological diagnosis of spindle cell sarcoma was made and was advised to excise.

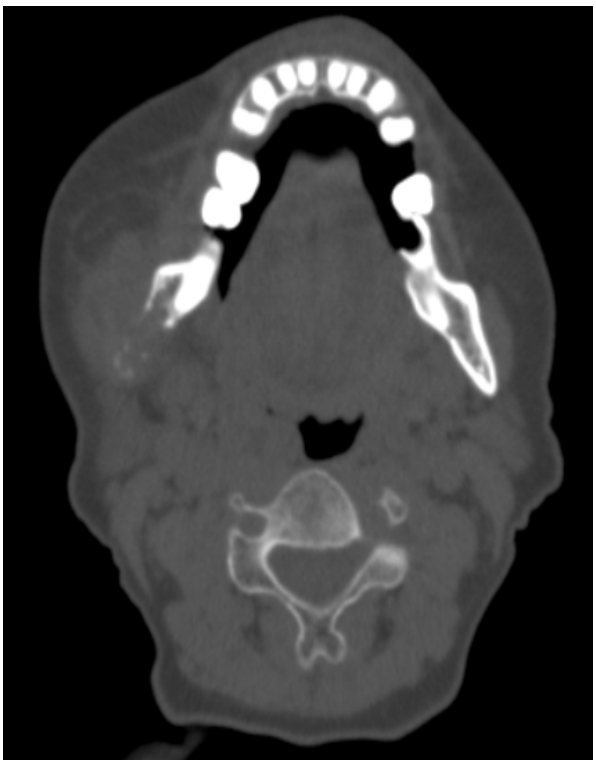

Fig. 8. CT axial image-Bone window

The ultrasound scan of the neck showed few prominent lymph nodes in the right-side level II with preserved fatty hilum and the largest lymph node was 6mm x 17mm in size. Subsequently, patient underwent chest radiography, ultrasound scan of abdomen and CT scan of the chest and abdomen but none of them showed any abnormalities.

After a multidisciplinary meeting with the oncologist and the oral pathologist, it was decided to treat the patient with curative intent, with surgical ablation followed by adjuvant chemo-radiation. As the lesion was centered in the angle and ramus of mandible a right side hemi mandibulectomy was planned in view of resecting with adequate margins.

Histological evaluation of the post-surgical sample showed unencapsulated tumour comprising spindle cells arranged in long interlacing fascicles in most areas. Cells show eosinophilic cytoplasm with indistinct cell borders. In most areas, cells show elongated, centrally placed and blunt ended nuclei whilst round to oval nuclei are seen in others. Moderate nuclear atypia was present in most cells with cells showing marked nuclear atypia in cellular areas. Focal areas showed epithelioid morphology. There was brisk mitotic activity amounting to 14 in 10 high power fields. There was evidence of tumour necrosis in cellular areas (less than 10%.). Scattered foci showed background myxoid stroma. Tumour cells invaded into adjacent skeletal muscles and adipose tissue (Fig. 9).

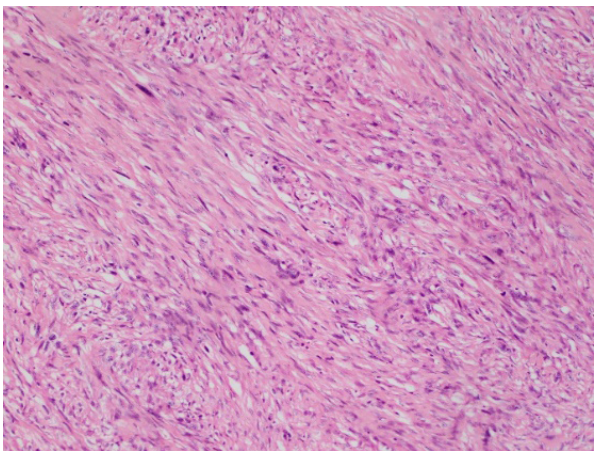

Fig. 9. Tumour cells (H&E, 20x)

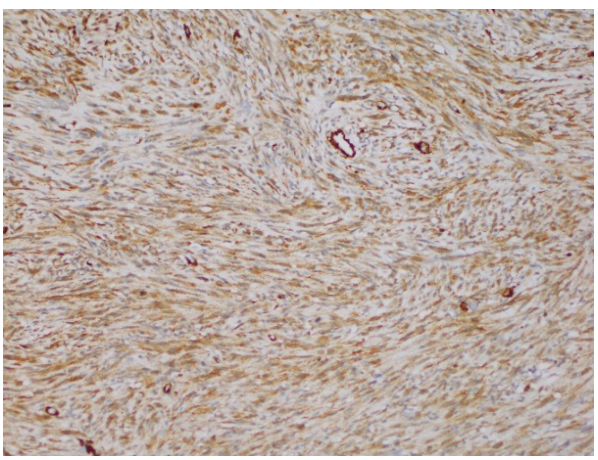

Fig. 10. Smooth muscle actin (IHC, 20x)

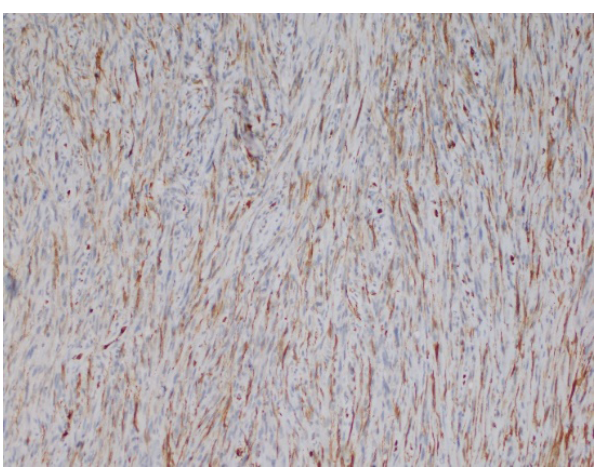

Fig. 11. Desmin (IHC, 20x)

Immunohistochemical studies (IHC) with smooth muscle actin showed strong cytoplasmic positivity in tumour cells (Fig. 10). Focal areas showed cytoplasmic

positivity for desmin (Fig. 11). Scattered nonspecific staining was present with S-100. These histopathological features together with IHC findings were consistent with a moderately differentiated leiomyosarcoma (G2). Histological evaluation of submandibular lymph nodes showed reactive lymphoid hyperplasia without evidence of metastatic disease.

Patient was subsequently transferred to the National Cancer Institute for specific treatments including chemotherapy.

Discussion

According to the recent review by Emanuela Palmerini et al., there is lack of knowledge on the RPMBS due to rarity of these tumours. Furthermore, there are very limited studies currently available in the literature on RPMBS.[1] Therefore, we considered sharing these two cases to increase the awareness among clinicians who are involving in the process of clinical, radiological and histological diagnosis of primary leiomyosarcoma of bones.

When considering the RPMBS, the differential diagnoses that should be kept in mind, include metastatic leiomyosarcoma from another site, primary undifferentiated pleomorphic sarcoma of bone, fibroblastic osteosarcoma, and metastatic sarcomatoid carcinoma.[7] Bone lymphoma may present with similar imaging findings to leiomyosarcomas. Therefore, bone lymphoma is one of the differential diagnoses considering the imaging findings alone. Further, lytic lesions with nonspecific imaging features of primary or secondary bone lesions may be considered as differential diagnoses on individual basis.[4] Metastatic leiomyosarcoma, especially from genitourinary tract or bowel need to be ruled out during the investigation process. In these two cases, possible primary sites of leiomyosarcoma were excluded with imaging modalities including CT scan of the chest and abdomen.

In the first patient, the bone lesion was seen in the left distal femur, who presented with a pathological fracture in the absence of a significant trauma to the affected limb. The plain X ray of the affected bone showed a lytic lesion with minimal expansion involving the distal meta-diaphyseal region of the left femur with extension in to the epiphysis, associated with a soft tissue component and an aggressive type of periosteal reaction. In a retrospective study done in Brazil, the most commonly affected bone site was the distal femur (31.7% cases), followed by the proximal femur (27.3% cases), proximal humerus (13.7% cases) and distal ulna (13.7% cases), proximal tibia (9.1% cases) and pelvis (4.5% of cases).[8]

In one case series, the metaphysis was involved in all cases with extension into epiphysis, diaphysis or both. In the same study, all long bone lesions showed osteolysis associated with variable degree of aggressive features including endosteal scalloping, permeation, ill-defined margins and lack of sclerosis. None of the lesions measured less than 7 cm in length, with average length being 11cm.[9] Longitudinal/elongated type of growth of long bone leiomyosarcoma also observed in other studies.[10] According to E. Santini-Araujo et al. these lesions showed high preference to grow in the longitudinal length relative to the medio-lateral expansion.[4] Most of these X ray features were comparable with our patient's X ray findings and the length of the lesion was approximately 10cm.

On MR images, most typical osteolytic lesions of long bones showed predominantly iso- or hyperintensity on T2-weighted spin echo sequences rather than heterogeneity associated with areas of iso- and hypointensity, in relation to fat. However, one study concluded that the MR imaging features of bone leiomyosarcoma are of T2 shortening in relation to the fat on conventional and fast spin echo sequences, manifesting as hypointensity. In that study, bone lesions show T2-weighted heterogenicity associated with areas of iso- and hypointensity in relation to fat.[9] Jiufa Cui et al. also mentioned that the lesions are not very hyperintense on T2-weighted images.[10] Similar signal heterogenicity was observed on T2-weighted sequences in our patient with distal femoral lesion. One case of bone leiomyosarcoma revealed fluid-fluid levels on MR images according to López Soriano et al. Further, it was the first case report mentioned about fluid-fluid levels on MRI in bone leiomyosarcoma. Therefore, the differential diagnoses for the presence of fluid-fluid levels in a bone tumour should include leiomyosarcoma.[11] However, this rare MRI appearance was not seen in our patient.

A study done in China revealed an epiphyseal involvement with subchondral bony extension in all cases of long bone leiomyosarcomas in their study. Other tumour characteristics include aggressiveness and extensive soft tissue oedema in relation to the primary lesion. This type of imaging features can be aided in the diagnosis of leiomyosarcoma of bones.[10] In our patient, the lesion was an expansile lobulated lesion with an epiphyseal extension. There was a cortical disruption with an extra osseous component as well. In addition, there was subcortical extension with knee joint involvement along the medial femoral condyle without knee joint effusion.

Due to relative paucity of smooth muscles in the maxillofacial skeleton, primary leiomyosarcomas in this area are exceedingly rare. There are very few reported cases of primary leiomyosarcoma arising in the mandible.[12]

LMSs of the oral cavity are usually painless lesions, presenting as swelling of the affected area leading to diagnostic difficulties as they mimic other common oral pathologies.[12] Absence of characteristic symptoms leading to challenges in the diagnosis and therapeutic management in maxillofacial leiomyosarcomas.[5] In one case series published by H. Amarapala et al, mod-

erately larger lesions mimicked an ameloblastoma or myxoma.[13]

In early stages, the mandibular leiomyosarcomas can be presented commonly with symptoms such as loss or mobility of teeth and gingival swelling or increase in volume.[14] Our patient with the mandibular lesion, had cheek swelling which gradually increased over the time. The orthopantomogram findings include a well-defined expansile lytic lesion with cortical destruction involving the mandible associated with complete destruction of the condyle on the right side. However, usual plain X ray features are of poorly defined lytic lesion with cortical destruction. The final diagnosis should be based on histopathologic and immunohistochemical features.[14]

As Dunfee et al. mentioned, specific diagnosis is not necessarily provided by radiological imaging, though, imaging should help to narrow-down the differential diagnoses of mandibular LMSs.[15]

Chemotherapy is one of the major treatment options for bone leiomyosarcomas. Palliative therapy is mainly reserved for patients with metastatic disease.[16-18] Our two patients were transferred for specialized cancer management center and started on chemotherapy. Recurrence rate and metastasis rate are directly correlate with the histological grade of LMSs while prognosis may be better than for other primary bone sarcomas of the same grade in non-metastatic patients.[4]

Both two patients were transferred to a cancer specific treatment institution after diagnosis of the disease condition. Therefore, we have limitations of the follow up of these two patients, with regard to their specific management aspects.

Conclusion

Primary leiomyosarcoma of bones is very rare. Imaging features are helpful in the evaluation of such conditions. However, final diagnosis should be based on histopathologic and immunohistochemical features.

Declarations

Funding

This research received no external funding.

Author contributions

Conceptualization, W.D.D.; Methodology, W.D.D.; Formal Analysis, W.D.D., D.R.S. and A.A.G.H.A.; Investigation, W.D.D., D.R.S., A.A.G.H.A., R.L.P.R.L. and I.W.G.A.L.M.; Resources, R.S., P.A.G.N. and R.M.A.S.R.; Data Curation, W.D.D., D.R.S. and A.A.G.H.A.; Writing – Original Draft Preparation, W.D.D.; Writing – Review & Editing, W.D.D., D.R.S., A.A.G.H.A., P.L.P.R.L. and I.W.G.A.L.M.; Visualization, W.D.D.; Supervision, R.S., P.A.G.N. and R.M.A.S.R.; Project Administration, W.D.D.

Conflicts of interest

The authors declare no conflict of interest.

Data availability

Data is available with the corresponding author on reasonable request.

Ethical consideration

Informed consent was taken from the patients and data was used anonymously.

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