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Intramedullary/intraosseous myelolipoma in a patient with pathologic fracture

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Abstract

Background: Intramedullary lipomatous tumors are rare and mostly reported in the metaphysis of the femur, tibia, and fibula. Myelolipomas are very rare tumors composed of adipose tissue and hematopoietic cells commonly reported in adrenal gland. We report the first reported case of intraosseous myelolipoma with a pathologic fracture in a young woman.

Case presentation: Patient is a young woman who carried a diagnosis of systemic lupus erythematosus, antiphospholipid syndrome, and hyperparathyroidism. Radiologic studies were done after the patient reported right lower leg pain lasting for a month. Radiologic examination showed a large osteolytic lesions with pathologic fracture affecting the medial aspect of the proximal tibia with extensive soft tissue calcification. The initial clinical and radiographic suspicion was brown tumor secondary to the hyperparathyroidism. Curettage of the lesion yielded large fragments of mature adipose tissue punctuated by a variable amount of mature hematopoietic cells. The histopathologic features were suggestive of myelolipoma. The overall radiographic and histopathologic features supported a diagnosis of myelolipoma. The diagnosis of intraosseous myelolipoma can be challenging in small samples such as core biopsies.

Conclusions: The differential diagnoses of intraosseous myelolipoma include normal bone marrow, intramedullary hematopoiesis, and other benign lesions. The gold standard diagnosis is histopathologic examination. However, clinical and radiographic features have important roles in the diagnosis of this rare lesion. Due to the rarity of this tumor and lack of formal guidelines for management, the case-to-case basis treatment is recommended.

Keywords: Intraosseous, tibia, myelolipoma, pathologic fracture, lipoma

Introduction

Myelolipoma is an infrequent benign mesenchymal tumor that is comprised of mature adipose tissue mixed with hematopoietic components and is usually found in the adrenal gland. Myelolipomas have been described in extra-adrenal sites such as the stomach, liver, mediastinum and kidneys but are extremely rare inside the bone (Sawhney et al., 2006; Kenney et al., 1998; Wood et al., 2013; Jaewon et al., 2019). The absence of hematopoetic elements differentiates myelolipomas from intraosseous lipomas. Myelolipoma is a rare entity and most frequently located in the adrenal glands (Plaut, 1958). Approximately 100 extra-adrenal myelolipomas (EAMLs) have been reported, most often in the abdomen, retroperitoneum, and mediastinum (Baker et al., 2012). Most patient are asymptomatic, and the tumor is nonfunctional. However, myelolipoma can grow in size and undergo hemorrhage and necrosis. Also, depending on the site and size of the lesion, myelolipomas can cause signs and symptoms of pressure on other parts of body. Pain and swelling are the most common symptoms when clinical manifestations present. Other locations are uncommon and mostly asymptomatic (Wen et al., 2015; Bokhari et al., 2020; Barman et al., 2014). Intra-osseous

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myelolipomas (IOML) are extremely rare with only 7 cases reported in the English and Non-English literature (Jaewon et al., 2019; Wen et al., 2015; Papapietro et al., 2009; Sundaram et al., 2007; Chiarini et al., 1992; Selye & Stone, 1950; Sakai et al., 2021). Considering the very low incidence of this tumor in bone, it is rarely considered in the differential diagnosis of intraosseous tumors. Herein, we present a case of a primary IOML and will review the 7 previously reported cases in order to increase the awareness of diagnostic criteria of this rare tumor.

Case Presentation

We report a case of a 25 years old female with a complicated past medical history including longstanding systemic lupus erythematosus (SLE), lupus nephritis and associated end-stage renal disease (ESRD), secondary hyperparathyroidism, seizure, and deep venous thrombosis (DVT). The patient reported unilateral right leg pain for one month. Radiographs showed large lytic lesions throughout the proximal two third of left tibia with the largest lesions located on the anterior and proximal aspects. The right tibia also showed large lytic lesions involving the mid to distal fibula and the proximal 2/3 of the tibia (Fig. 1), with pathologic fractures affecting the tibiae, bilaterally. The radiographs also showed extensive soft tissue and atherosclerotic calcification of the popliteal, anterior and posterior tibial arteries. The patient underwent bilateral open reduction and internal fixation (ORIF) by orthopedic surgery.

Histologically, curettage of the left tibial lesion yielded large fragments of mature adipose tissue populated by variable amounts of mature hematopoietic cells. No bone trabeculae were identified (Fig. 2). The overall radiographic and histopathologic features supported a diagnosis of IOML. The post-op laboratory work up showed vitamin D deficiency, and severe secondary hyperparathyroidism with parathyroid hormone (PTH) levels of 4494 pg/mL (normal range 6.0-48.0 pg/mL). Consequently, she underwent 3.5-gland parathyroidectomy with half-gland implantation into the neck, and this decreased the PTH level to 129.6 pg/mL in a 4-week follow up. To complete the work-up, a bone marrow biopsy was done and it was unremarkable except for a mild increase in iron stores. One month later, radiological studies showed a closed, displaced right supracondylar femur fracture which was reduced and internally fixed. No additional lesions compatible with myelolipoma were identified. The 6-month follow-up showed diffuse osseous demineralization with no fractures or tumoral lesions but there were mild degenerative changes throughout the foot along with marked vascular and soft tissue calcifications. The patient continued on her treatment for lupus, DVT and ESRD and has not had any sign of myelolipoma recurrence to date.

Discussion

Myelolipomas are relatively unusual, benign tumors comprised of a mixture of mature adipose and hematopoietic tissue most commonly found in adrenal

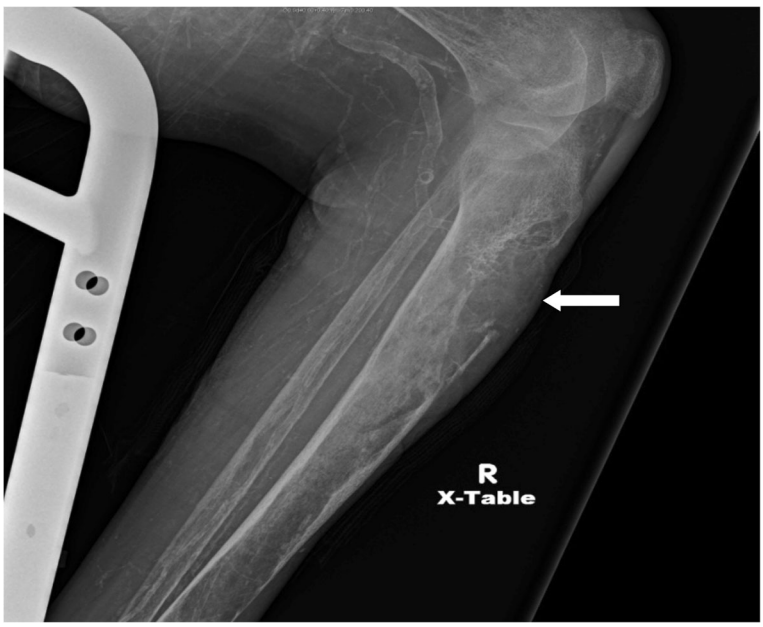

Fig. 1 Radiologic examination showed a large osteolytic lesion with pathologic fracture affecting the medial aspect of the proximal tibia with extensive soft tissue calcification

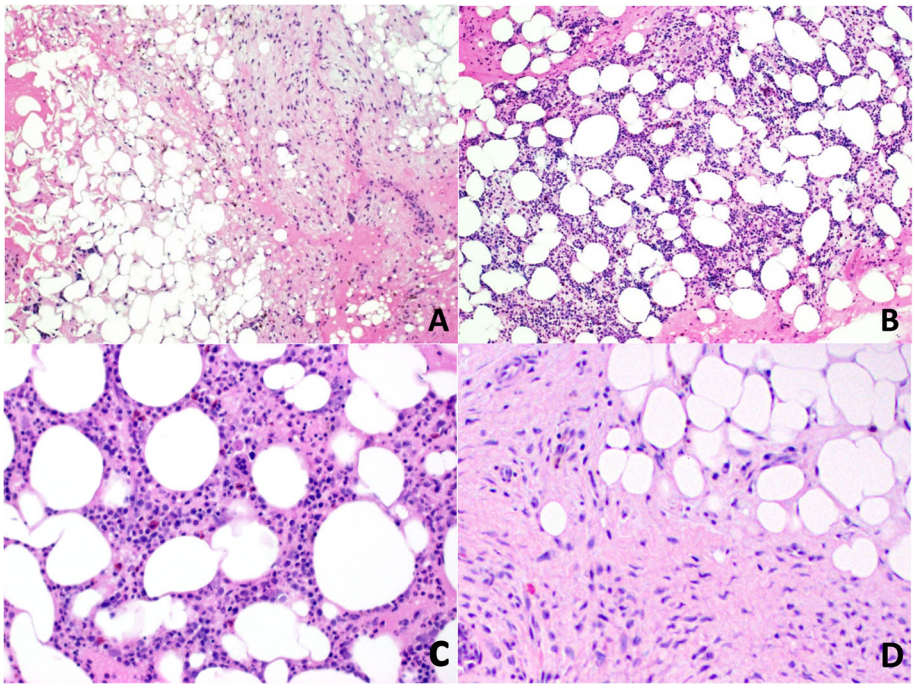

Fig. 2 Hematoxylin and Eosin staining (A: 4x10, B: 10x10, C & D: 20x10) A: Curettage sections yielded fragments of mature adipose tissue. B, C: Variable amount of normocellular mature hematopoietic cells from all three lineages are present. D: Mature adipose and fibrotic tissue is present. No osteoclastic giant cells, hemorrhage or bony tissue was identified

glands (Sawhney et al., 2006; Kenney et al., 1998). EAMLs are rare, with only a handful of reported cases (Wood et al., 2013; Shen et al., 2014; Sagan et al., 2009; Fowler et al., 1982) and the retroperitoneum as the most common extra-adrenal location (Kenney et al., 1998). Our literature review reveals that IOML are extremely rare, with only seven cases reported in the period of 1992-2019 in English and non-English literature (Table 1) (Wen et al., 2015; Papapietro et al., 2009; Sundaram et al., 2007; Chiarini et al., 1992; Sakai et al., 2021).

Myelolipomas usually happen in late adulthood and have no gender predilection. The reported intra-osseous cases showed a variety of ages and no gender predilection (Bokhari et al., 2020). Even though most of myelolipomas are asymptomatic and may be incidental findings (Bokhari et al., 2020; Hakim & Rozeik, 2014), all the reviewed IOML patients were symptomatic and the workups were initiated due to their signs or symptoms.

Several etiologies have been proposed for adrenal myelolipomas, including the degeneration of hyperplastic nodules or adrenal adenomas or myeloid and mesenchymal cell hyperplasia, which are erroneously displaced during embryogenesis. The literature also suggests that myelolipomas can result from stress-induced metaplasia of the reticuloendothelial tissue or prolonged stimulation of erythropoiesis in chronic anemia (Wilhelmus et al., 1981). The other possible proposed etiologies include seeded bone marrow emboli, metaplasia of adrenal stromal cells, or the metaplasia of reticuloendothelial cells (Merchant et al., 2002).

However, all proposed etiologies rely on only hypotheses due to the rarity of this tumor. Bishop et al. suggested a clonal origin for myelolipoma (Bishop et al., 2006). Seyle and his colleages were the first to produce myeloid tissue in the adrenal glands of rats by injecting necrotic tissue into those glands, and this suggested that hematopoetic metaplasia may be caused by hormonal stimulation of the adrenocortical tissue (Selye & Stone, 1950).

Stressful events such as cancers, renal diseases, and cardiac lesions may also contribute to this transformation (Selye & Stone, 1950). Feng et al. hypothesized that the stimulation of mesenchymal endothelial cells produce adipose tissue and that the adipocytes become inflammatory as they mature, which in turn stimulates the neighboring adrenal cortex which releases granulocyte colony-stimulating factor (G-CSF) which recruits the circulating hematopoietic progenitors (Feng et al., 2013). Overall, most of the authors accept the hypothesis that the metaplasia occurs in the reticuloendothelial cells of the blood capillaries after a stressful stimulus (Decmann et al., 2018). However, due to the extreme rarity of this tumor in bone, no hypothesis for the etiology of IOML has been suggested. In our patient, a long history of chronic autoimmune disease and secondary hyperparathyroidism could have triggered a stressful event which

Table 1 compares clinicopathological features, treatments, and follow-ups of the intraosseous myelolipoma cases reported to date

Authors	Age/Gender	Signs/symptoms	Radiographic findings	Pathologic findings	Treatment	Follow-up
Sakai T. et al 2021	25/F	Slow growing mass (for 10 years) on distal femur	The X-ray showed a 20 cm osteolytic lesion without bony demarcation and periosteal reaction with sunburst appearance. CT scan showed a destructive lesion with invasive progression. MRI showed high signal intensity on T1 and T2 and low signal intensity on the fat-suppression images.	Needle and open biopsies showed fatty and hematopoietic tissue with no atypia.	Hip disarticulation for complete tumor resection was considered but was not done due to the patient's comorbidities and high risk for surgery.	No change in tumor size after two years.
C. Jaewon et al 2019	61/M	Slow growing mass with swelling on mandible	The panoramic radiograph showed multilocular and radiolucent lesions of maxilla and mandible. CT scan showed trabeculation of lesions. Radionuclide bone scan showed the lesion is cold.	Mature adipose tissue and hematopoietic elements.	After the incisional bone biopsy was done for diagnosis, it was decided to conserve the lesion due to painlessness and wide range of lesions.	Not available
Wen J et al., 2015	18/M	Left chest mass	CT scan showed a well-circumscribed osseous mass with heterogeneous low density derived from the anterior 6th rib with a sclerotic rim	Histological examination revealed mature adipocytes mixed with hemopoietic cells consisting of trilineage elements: myeloid, erythroid and megakaryocytic cells, and local reticular fibers	Radical excision of the mass and part of costal pleura and 6^{th} rib	2 years follow-up revealed no complication or tumor recurrence
Papapietro N., 2009	80/M	Chronic right hip pain and a history of treated prostatic carcinoma	Radiographs revealed a well-defined intramedullary osteolytic lesion found in the intertrochanteric region, without cortical erosion; CT scan revealed an intraosseous hypodense lesion with fat attenuation. No cortical erosion or cortical deformity was observed. A post-contrast CT scan revealed no enhancement of the lesion.	CT-guided percutaneous needle biopsy and histology revealed a lesion composed of mature adipose tissue with areas of hematopoietic tissue. The adipocytes showed no cellular atypia or mitotic activity, and the hematopoietic tissue included erythroid and megakaryocytic elements as well as lymphocytes. No bony spicules or sinusoids	Intralesional curettage of the intertrochanteric region and filled with homologous bone and autologous platelet-rich gel.	Six months postoperative CT scan showed no evidence of recurrence of myelolipoma.

Table 1 compares clinicopathological features, treatments, and follow-ups of the intraosseous myelolipoma cases reported to date *(Continued)*

Authors	Age/Gender	Signs/symptoms	Radiographic findings	Pathologic findings	Treatment	Follow-up
				were identified.		
Sundaram M., 2007	35/F	Right hip pain	The radiographs demonstrated a 4 cm × 4 cm well-marginated mixed sclerotic and osteolytic lesion in the roof of the right acetabulum favoring the diagnosis of fibrous dysplasia.	The histology confirmed neither fibrous dysplasia nor lipoma but contained mildly hypercellular/ normocellular marrow with normal hematopoietic elements	Intra-lesional curettage	Symptoms decreased on follow-up
	51/ not mentioned	Diabetic with hip pain CT scan confirmed a well-confined osteolytic lesion in the proximal femur.	CT scan confirmed a well-confined osteolytic lesion in the proximal femur.	Biopsy of the lesion showed hematopoietic bone marrow with occasional fat cells. Subsequently, the patient had a stress fracture of the lesion and resection specimen demonstrated hematopoietic marrow with mature red and white cell lines. There was no atypia, no granulomatous changes, and no fibrosis.	Data not available	Data not available
Chiarini L, 1992	Not mentioned/F	Right mandibular lesion which was grossly visible for 1 year.	Radiography showed presence of two dental elements within a total bone inclusion. There was a large translucent area between the lower mandibular canal and the two upper dental elements. This radiolucent area was not well-circumscribed and is homogenous with no septation. The homogeneity is consistent with a cystic structure. The second radiologic film reviewed (after biopsy result) confirms a similar contralateral translucent lesion with similar dimensions.	Histopathologic examination of the tissue showed adipose tissue and active myeloid tissue.	Excisional biopsy and extraction of the adjacent dental elements. A residual cavity was remained after the removal of mass and dental elements. Further physical examination and laboratory testing for possible extramedullary hematopoiesis was performed which was negative.	18 month follow up showed complete disappearance of the swelling. The follow up radiology documented a good healing of the tumor site.

stimulated the release of G-CSF to alter mesenchymal cells in the large areas of osseous demineralization. Alternatively, both of the IOML cases with mandibular and maxillary involvement, the lesions were close to the teeth, were multifocal, and were more extensive than the other reported IOMLs, suggesting the possibility of mesenchymal origins. However, given the low number of reported cases and limited available data, we are still not able to go beyond few reported hypotheses in considering the etiology of IOML.

On radiology, myelolipomas usually show a hypodense mass that may have a heterogeneous or homogeneous appearance. Distinguishing myelolipoma from other fat-containing tumors is difficult. Considering the different radiologic manifestations, it is nearly impossible to reach a definitive diagnosis without a histologic examination (Hakim & Rozeik, 2014; Decmann et al., 2018). The radiologic finding in our case showed multiple lytic lesions with a pathologic fracture but the correlation of this fracture with myelolipoma is doubtful given that the patient has a history of hyperparathyroidism, ESRD, and vitamin D deficiency. She also developed an additional pathologic fracture after the removal of myelolipoma and we suspect myelolipoma is more of a co-morbidity rather than a causal factor. In the reported cases, a variety of radiological findings were present but all were consistent with a low density or osteolytic lesion ranging from a hypodense foci to a tumoral mass (Table 1). Most patients presented with a single intraosseous lesion with the exception of the two cases on the maxilla and mandible which presented with multiple, wide lesions (Jaewon et al., 2019; Chiarini et al., 1992). Sundaram et al. reported that the first reported Italian case of IOML did not have a pre-operative radiology study but in fact such a study was performed (Sundaram et al., 2007; Chiarini et al., 1992). Thus, all reported cases had radiological work-ups before the excisional or curettage procedures. Nevertheless, myelolipoma was confirmed only based on the histopathologic examination of the tissue.

To establish a diagnosis of myelolipoma, the presence of hematopoietic and adipose tissue should not have any justification in that organ and the formation of the myeloadipose tissue in the site should not be secondary to a physiologic hematopoietic hyperplastic response (Chiarini et al., 1992). When myelolipoma occurs in extra-osseous locations, a high suspicion for that diagnosis is raised by a needle biopsy followed by a pathological examination, which shows the mature adipose tissue with trilineage hematopoietic elements (Bokhari et al., 2020; Yang et al., 1992). However, in IOML, diagnosis is further challenged by the presence of adipose tissue as a part of the bone marrow and the seldom presence of hematopoietic cells mixed with adipocytes. The differential diagnosis for an intra-osseous tumor-like lesion is vast and heavily dependent on location, age, and radiologic findings. Myelolipomas are composed of both mature fat and hematopoietic elements and the diagnosis is made based on ruling out the other histopathological counterparts (Sundaram et al., 2007). The biopsy findings can resemble focal hematopoietic hyperplasia (FHH) which is histologically known to show hyperplastic marrow elements merging with fatty marrow with no hematopoietic dyspoiesis or malignancy (Wen et al., 2015; Galindo et al., 1998). In contrast, myelolipomas show normal cellularity. All reported IOML cases showed marrow cellularity within the normal range for the patient's age. Intra-osseous lipomas are one of the rarest bone tumors and while they mostly occur in the lower limbs, they can occur in any bone. The histologic examination of these tumors can show different stages of lipocyte involution but generally do not show any hematopoietic cells (Milgram & Intraosseous lipomas., 1988). Other differential diagnoses to consider include marrow hyperplasia in response to chronic hemolysis or excessive usage of blood cells due to an underlying disease. However, anemia and hepatosplenomegaly are usually associated with these cases. Hyperplasia of bone marrow can be seen in adults with no chronic hemolysis (Shellock et al., 1992). This pattern of hyperplasia shows the dominancy of the red component of bone marrow in contrast to myelolipoma, which usually shows the normal proportion of hematopoietic lineages among the different lineages.

To date, the reported locations of myelolipoma include humerus, acetabulum, femur, rib, mandible, and maxilla. We report the first case of tibial myelolipoma accompanied with a pathologic fracture. The follow up of our patient did not show any evidence of myelolipoma recurrence but did show multiple fibular fractures which led the clinician to remove the parathyroid glands in order to prevent future pathologic fractures.

IOML is managed conservatively or surgically depending on the diagnostic certainty, the location of the lesion, and the disease progression. Due to the rare incidence of IOML, the existing literature contains no treatment guidelines. In all the cases where follow-up data was available, none of the patients showed recurrence or a malignant transformation.

Conclusion

IOML is a benign and extremely rare tumor composed of adipose and hematopoietic tissue. The first case report of an intra-osseus myelolipoma is from an Italian dentistry journal in 1992 which was either misinterpreted or not further studied due to the unavailability of an English translation. We are presenting the largest literature review of IOML in both the English and non-English literature. Due to the lack of formal guidelines

for managing IOMLs, the case-to-case basis treatment has been recommended. It appears to us that surgical excision or curetting are necessary for diagnostic purposes and may reduce the mass effect or the associated symptoms. The risk of recurrence after excision is minimal and no malignant transformation has been reported. However, more case reports are needed to specify the characteristics of this lesion and develop more consistent and certain diagnostic criteria with treatment protocols.

Abbreviations

EAML: Extra-adrenal myelolipomas; IOML: Intra-osseous myelolipomas; SLE: Systemic lupus erythematosus; ESRD: End-stage renal disease; ORIF: Open reduction and internal fixation; PTH: Parathyroid hormone; G-CSF: Granulocyte colony-stimulating factor; FHH: Focal hematopoietic hyperplasia

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Authors' contributions

AA gathered the data and was a major contributor in writing the manuscript. SNA reviewed the existing literature and was a major contributor un the writing the manuscript. MK helped with writing the manuscript. LH performed the histological examination of the tissue and edited the manuscript. KMF was the senior author and made did the histologic examination, made the final diagnosis was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

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Declarations

Ethics approval and consent to participate

OUHSC does not require IRB for case reports with no identification information.

Consent for publication

Not applicable. No identifiable information/ clinical picture is provided in the manuscript.

Competing interests

None

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