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Case Report

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Case Report of a Low-Grade Primary Leiomyosarcoma of the Proximal Fibula in A Young Woman

Mary C. Hamati, M.D.[1]*, Geoffrey W. Siegel, M.D.[2]

[1]Post-doctoral Research Fellow, Orthopedic Research Center, Department of Orthopedic Surgery, University of Colorado Anschutz Medical Campus, USA.
[2]University of Michigan Assistant Professor, Orthopaedic Surgery Musculoskeletal Oncology, USA.

***Corresponding author:** Mary C. Hamati, Post-doctoral Research Fellow, Orthopedic Research Center, Department of Orthopedic Surgery, University of Colorado Anschutz Medical Campus, USA. Email: mchamati@outlook.com; Geoffrey W. Siegel, gsiegel@med.umich.edu

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Abstract

Introduction: *Primary leiomyosarcoma of the bone (PLB) is a rare malignant tumor. Majority of cases are high-grade and have a poor prognosis. Due to the rarity, the pathophysiology is not well understood. It most commonly occurs in the distal femur or proximal tibia. Only seven cases of the fibula have been reported (6 distal, 1 proximal). This is the second reported case of PLB in the proximal fibula.*

Case Report: *A 43-year-old white woman presented to the emergency department for one week of worsening lower left leg pain. Plain films showed an osteolytic lesion within the proximal fibula. The patient underwent complete staging work-up and image-guided biopsy and was diagnosed with a low-grade primary leiomyosarcoma of the bone without metastasis. She underwent surgical resection with negative margins and is currently undergoing follow up protocol. She is free of disease at this time.*

Conclusion: *This is a rare report of a poorly understood primary bone smooth cell sarcoma. This case is particularly unique due to the rare location and low-grade nature of the tumor. By reporting this case we hope to add to the demographic characteristics, presentation, microscopic and immunohistochemical diagnosis, management, and prognosis for PLB. Furthermore, we report a comprehensive review of the literature and comment on different management protocols world-wide.*

Keywords: *primary leiomyosarcoma of the bone, interosseous leiomyosarcoma, case report, smooth-muscle sarcoma, orthopaedic surgery, musculoskeletal oncology.*

Introduction

Primary leiomyosarcoma (LMS) of bone (PLB) is an uncommon malignant mesenchymal-derived lesion with a poor prognosis first described by Evans and Sanerkin in 1965 [1]. The majority of tumors are found in long bones (femur and tibia), specifically in the metaphysis and epiphysis [2]. This case report documents the diagnosis and management of a 43-year-old woman diagnosed with PLB in the metadiaphysis of the proximal fibula. There have been seven reported cases of PLB of the fibula, with only one located in the proximal fibula [2,3,4,5,6].

Patients most commonly present with localized pain and an osteolytic lesion with a permeative pattern exhibiting aggressive characteristics superscript. On magnetic resonance imaging (MRI) these lesions usually appear hypointense on T1 weighted imaging and hyperintense or isointense on T2 weighted imaging[2]. Diagnosis is based on histopathologic evidence that demonstrates atypical sheet-like proliferation of spindle cells arranged in intersecting fascicles with focal malignant fibrous histiocytoma-like areas, usually without osteoid [2]. On IHC staining, they are commonly positive for smooth muscle actin, HHF35, caldesmon, and desmin [2]. Known associated risk factors for primary bone sarcomas include: therapeutic radiation, Paget disease, orthopedic implant, chemotherapy, Epstein Barr virus, hereditary retinoblastoma, and bone infarct [2,7,8]. Two theories for pathogenesis are suggested: (1) tumor cells arise from the smooth muscle cells of blood

vessels, and (2) tumor cells arise from perivascular myofibroblasts or mesenchymal fibroblasts [2].

The most comprehensive review of the literature was done by Adelani et al [2]. They compiled data on 104 previously documented cases (38 articles) and three unique cases of primary LMS of extra-gnathic bone from 1965 to 2009. Pain was the most common presenting symptom, men and women were affected equally between their 4th and 7th decades. A review completed by Miura et al reported on 136 cases published before 2001 [9]. Twenty-three of their 58 articles were included in Adelani et al's review. The remaining 35 articles included PLB in the maxilla and mandible and non-English literature. PLB occurring above the neck is found to have different incidence, metastases locations, and mortality rates than extra-gnathic bone; therefore, these cases are no longer analyzed together [10].

Recently published literature attempts to evaluate prognostic factors and the role of chemotherapy. Case series from single-institutions and oncology databases are accumulating in the literature **(Table 1)** [2-5,11,12].

	2009 Adelani [2]	**2011 Rekhi [12]**	**2012 Brewer [4]**	**2016 Mori [5]**	**2019 Berner [3]**	**2019 Zumarraga [11]**
Country	USA	India	UK	Japan	Norway	Brazil
Total patients	107	8	31	48	14	22
Gender, n (%)						
Male	56 (52)	6 (75)	12 (39)	19 (40)	7 (50)	10 (45)
Female	51 (48)	2 (25)	19 (61)	29 (60)	7 (50)	12 (55)
Age, (median)	9-87 (47)	29-59 (40)	9-88 (46)	14-88		17-73
Mean		43		52		45.5
≤40					3 (21)	
>40					11 (79)	
Size, mean (cm)	NR	8.4 (n=4)	NR	8.3	8	
Median			8		9	
<10 cm						15 (68)
≥10 cm						7 (32)
Grade, n (%)	85 (79)	8 (100)	31 (100)	48 (100)	14 (100)	22 (100)
High	62 (73)	6 (75)	26 (84)	NR	12 (86)	20 (91)
Low	23 (27)	2 (25)	5 (16)		2 (14)	2 (9)
Metastasis at diagnosis, n (%)	8 (17) (n= 48)	0 (0)	6 (19)	7 (15)	3 (21)	NR
Surgery, n (%)	**87 (81)**	**5 (63)**	**30 (97)**	**35 (73)**		**22 (100)**
Resection	64 (74)	2 (40)	2 (7)	6 (17)		17 (77)
Amputation	22 (25)	3 (60)	8 (27)	7 (20)		5 (23)
Endoprosthesis replacement	1 (1)		20 (67)	22 (63)		
CT§, n (%)	**33 (31)**	**1 (13)**	**18 (58)**	**25 (52)**		**15 (68)**
Neoadjuvant	12 (36)	0 (0)	17 (94)	3 (12)		0 (0)
Adjuvant	1 (3)	0 (0)	1 (6)	7 (28)		0 (0)
Both/N/A	20 (61)	1 (100)	0 (0)	15 (60)		15 (100)
Overall Survival						
5-year	59%	NR	62%	78%	36%*	59%
Recurrence, n (%)	**42¶ (39)**	**5 (63)**	**15 (50)**	**14 (29)**		**14 (64)**
Local	9 (21)	0 (0)	2 (13)	1 (7)		5 (36)
Distant	33 (79)	5 (100)	12 (80)	8 (57)		9 (64)
Both		0 (0)	1 (7)	5 (36)		

*For all primary spindle cell sarcomas
§Chemotherapy
¶Only included patients with a minimum of 2-year follow up

Table 1: Demographics and pooled data from reviews and large case series.

A study using the Norwegian Cancer Registry database reported PLB in 14 patients, however, much of their data is analyzed as a conglomeration of spindle cell sarcomas [3]. A single institution study from Brazil (22 cases) confirmed previous findings on demographics and 5-year survival [11]. Almost 70% of their patients received chemotherapy and had a recurrence rate of 64%. The Japanese Musculoskeletal Oncology group (48 cases) reported a female predominance and 5-year overall survival of 78% [5]. Single institution studies from the UK (31 cases) [4] and India (eight cases) [12] found a slight female and male predominance, respectively. Pathologic fractures have been reported in 20-42% of patients on presentation [2,3,4]. Metastasis at diagnosis ranges from 17-21% [2-5].

Rekhi et al reported zero patients with metastasis at diagnosis [12].

Due to the infrequency of PLB, characterization, imaging and pathologic findings, prognosis, and treatment are difficult to evaluate. This case report adds to the literature on PLB due to its unique location and low-grade nature.

Case Report

A 43-year-old female reported to the emergency department for a one-week history of left lower leg pain, weakness, and tingling, with no associated injury. The pain was a deep ache in nature with a severity of 6-7/10. Physical exam revealed no mass or tenderness to palpation. Her past medical history included anemia, arthritis, fibrocystic breast disease, gastroesophageal reflux disease, and hypertension (resolved). Her past surgical history included a hysterectomy with bilateral oophorectomy (2014, endometriosis), sinus surgery, gastric bypass, and cholecystectomy. The patient's family history is positive for skin cancer (father), multiple myeloma (mother), breast cancer (paternal grandmother), melanoma (maternal grandfather), and unspecified cancer (maternal grandmother). An x-ray showed a small lytic lesion within the proximal fibular diaphysis **(Figure 1)**. She was referred for outpatient follow up.

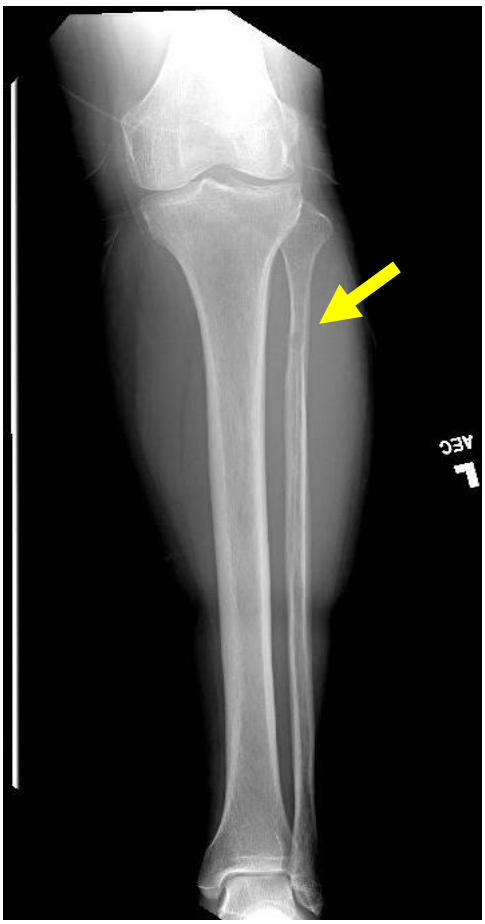
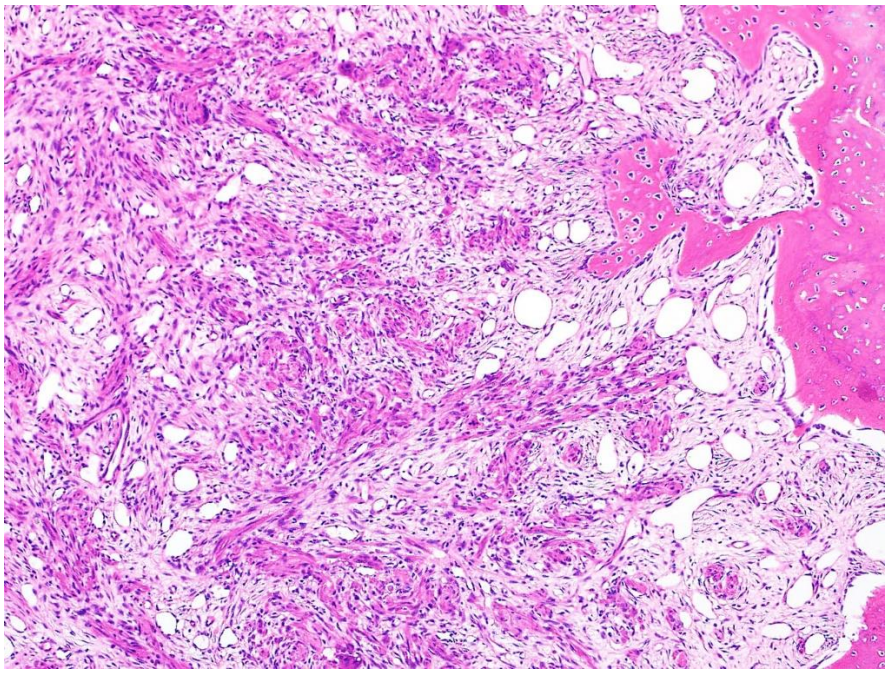


Figure 1: Original x-ray obtained Spring 2019 showing a small lytic area in the proximal fibula (yellow arrow).

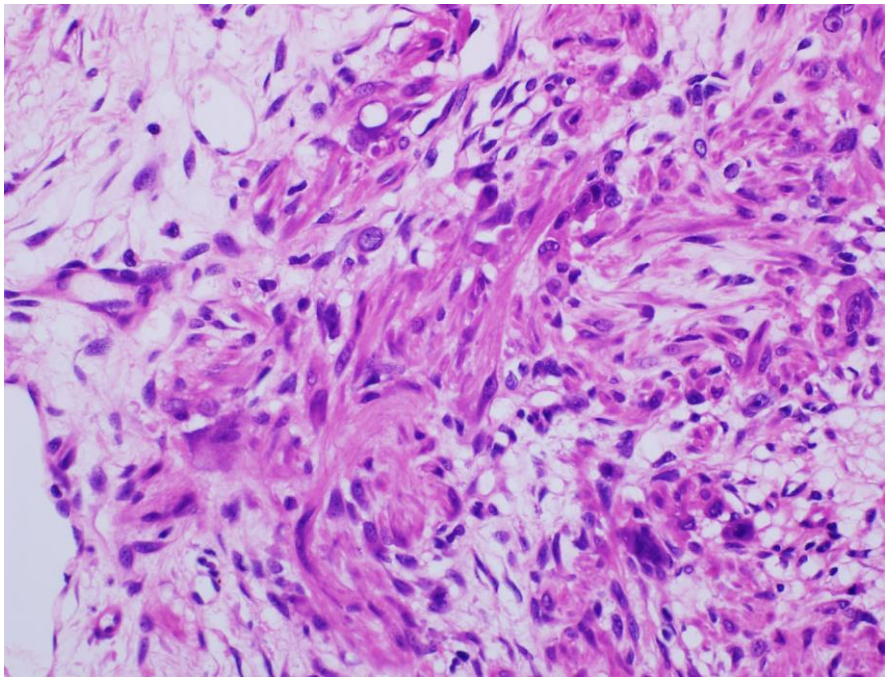
During follow up she reported worsening pain now radiating distally. MRI with and without gadolinium contrast demonstrated a marrow replacing, T2 hyperintense, T1 hypointense 3.0 cm lesion in the left proximal fibular metadiaphysis with surrounding muscular edema and posterior cortical breakthrough. Computed tomography (CT) demonstrated a cortically based, circumscribed, lucent lesion with periosteal reaction without evidence of a discrete soft tissue mass. A whole-body radionuclide bone imaging was ordered and showed a focal area of increased MDP uptake in the left proximal fibula consistent with a lytic lesion. Mild degenerative arthritis in the thoracolumbar spine and both knees was also evident. Differential at this time included a solid bony metastasis of unknown primary malignancy, or an aggressive primary bone lesion. A chest/abdomen/pelvis CT showed a 2 mm noncalcified right upper lobe nodule classified as indeterminant.

An image-guided biopsy was performed showing erratic spindle-cells (Figure 2A, 2B). IHC stains showed neoplastic cells positive for smooth muscle actin and caldesmon and negative for cytokeratin cocktail, ERG, SOX10, desmin, CD 117, STAT6, and TLE-1, confirming the diagnosis of a grade 1 leiomyosarcoma (pT1 NX, AJCC 8th edition).

Figure 2: Histologic examination under low- and high-power fields.



A: Low-power field showing neoplastic spindle cells.



B: High-power field showing neoplastic spindle cells.

The case was presented at the multidisciplinary sarcoma tumor board for treatment planning. Final treatment consisted of wide resection surgery resulting in negative margins. The incision was in line with the fibular shaft. After sharp dissection through the subcutaneous fat, we incised the posterior aspect of the fascia overlying the peroneal muscle compartment and identified the common peroneal nerve which was diligently protected throughout the case. An attempt was made to spare the fibular head (per pre-op MRI Planning) and the initial osteotomy was made at the fibular neck. However, intraoperative frozen section revealed scant atypical spindle cells concerning for a positive margin at the proximal end. The fibular head was skeletonized leaving a very small cuff of periosteum overlying the bone at the margin. A total of 12 centimeters was resected. The final surgical pathology report confirmed grade 1 PLB measuring 1.7 x 1.3 x 0.9 cm (Figure 3). Post-operative tumor board review recommended sarcoma surveillance with a chest imaging (X-ray with interspersed CTs due to the 2mm indeterminate lung nodule) every three months for two years, every four months for the third year, and every six months for the fourth and fifth year and an MRI of the tumor bed with gadolinium tumor protocol every six months for two years.

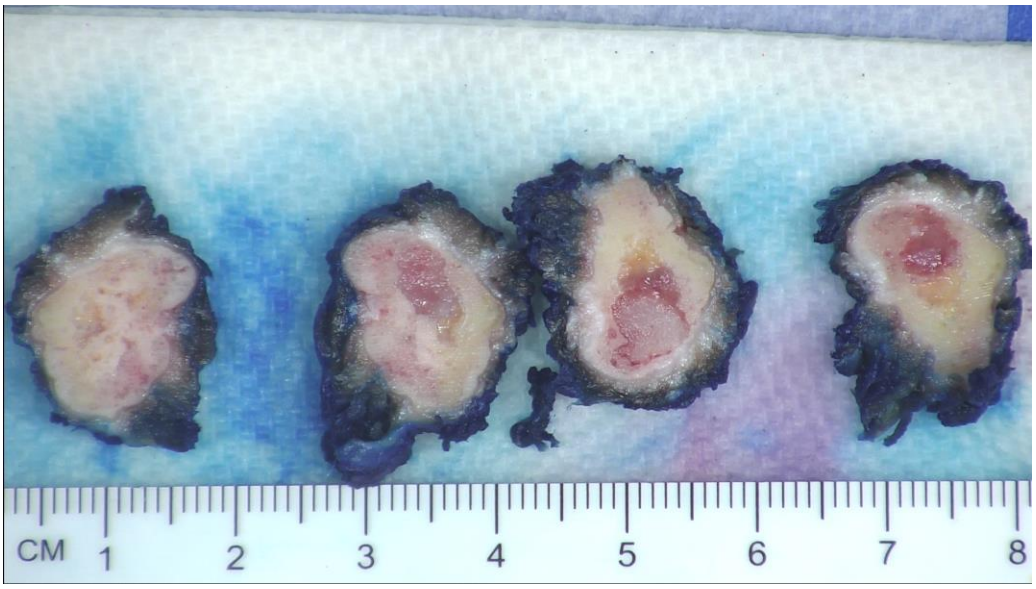


Figure 3: Gross tumor: pink-tan, soft and fleshy, white sclerotic and whorled-appearing cut surfaces.

At her three-month postoperative follow up she reported mild instability in the left knee, right lateral hip pain due to altered gait, and no other symptoms. Physical exam showed intact sensation in the peroneal nerve distribution and strength of the peroneal musculature and a well-healing surgical excision. X-ray (Figure 4) and chest CT were obtained. The chest CT demonstrated an unchanged 2 mm nodule. The patient remains tumor free ten-months postoperative.

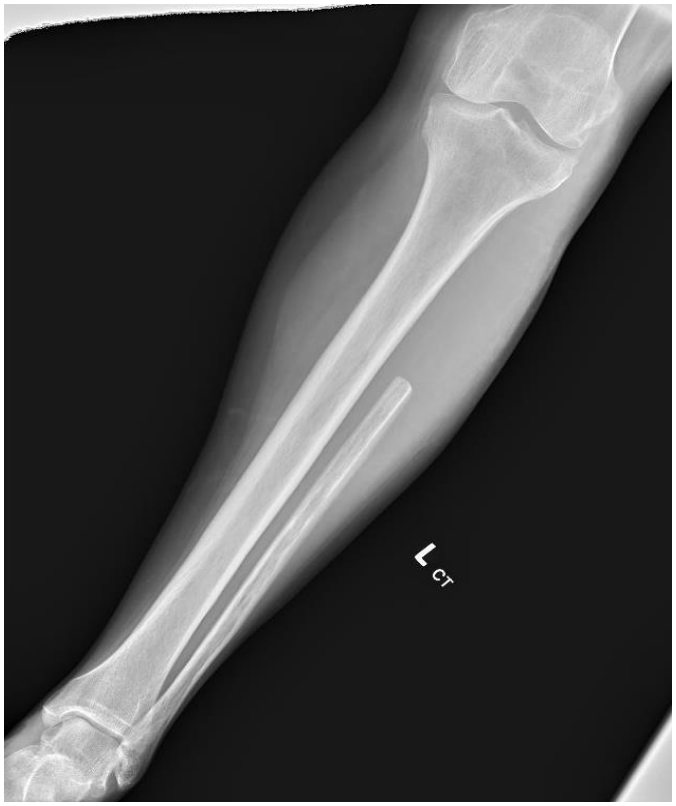


Figure 4: Postoperative 3-month x-ray of the left lower extremity.

Discussion

Due to the low incidence of PLB, prognostic factors and effective treatments are difficult to evaluate. From the available data, this patient is congruent with the classic presentation of PLB: focal bone pain presenting in her 40s. PLB typically presents as intramedullary osteolytic lesions with associated cortical destruction and extension into the soft tissue, as seen in our patient [2,9]. Low-grade PLB can demonstrate a sclerotic rim which is typical of non-ossifying fibroma or other benign etiologies, however no sclerotic rim was seen in this patient [2,6,13]. Interestingly, PLB presenting in the spine may not show lytic patterns on plain films or CT [7]. Mineralization on imaging has also

been reported in up to 20% of cases, although this is more typical of osteosarcoma [14]. Notably, one case study reported reactive sclerosis on CT which is not typical [15].

Gross pathology typically demonstrates white-gray tumor with areas of necrosis or hemorrhage, as seen with our patient [2,4]. Microscopically, low grade tumors have shown to have different attributes however, majority of tumors are high grade lesions (73-91%) [2-4,11,12]. Osteoclast-like giant cells have been reported in PLB [1,12,16,17]. In unclear cases, ultrastructural presence of smooth muscle differentiation can help distinguish between LMS and myofibroblastic sarcoma [2,16]. On IHC staining, our patient was positive for smooth muscle actin and caldesmin. Desmin staining was negative in our patient and has been reported positive in 50% [2] of patients with PLB, however, more recent case series reported 100% [11] and 75% [12] of their cases stained desmin positive.

Prognosis for PLB is bleak and prognostic factors are difficult to measure. As expected, prognosis has been shown to be closely related to tumor stage, with complete surgical resection as the proven treatment [2,3,5,11]. Amputations may be necessary for high grade tumors with neurovascular bundle infiltration. Berner et al reported high age, metastatic disease, and axial primary tumor predicted poor outcome for PLB, while pathologic fracture and large tumor size were associated with poor prognosis for all types of spindle cell sarcomas [4]. At the molecular level, one study of five cases measured genomic instability and found tumor cell chromatin loss was associated with the poor outcomes [18]. The large case series in Table 1 report similar 5-year overall survival as Adelani et al (59%) [2], except Mori et al [5] (78%). It is unclear why the survival rates differed (age, gender, and metastasis at diagnosis are comparable). This could be attributed to improved technology over time (2000-14 vs. 1960-2009). Another consideration is the lower rate of recurrence (29%) found in Mori et al's study (compared to 39% [2], 63% [12], 50% [4], and 64% [11]). About half of their patients received adjuvant chemotherapy however this did not improve overall survival and neoadjuvant chemotherapy (cisplatin-based per osteosarcoma protocol) did not show a good radiological or histological response, suggesting it is not effective [5].

Chemotherapy use is high in Brazil [11] and the UK [4] compared to the United States, as well. Eighteen of the 31 patients from the UK were treated with chemotherapy with only three patients achieving >90% necrosis [4]. Their findings suggested those who responded well to chemotherapy had better survival, although this was not statistically significant due to their small case numbers. One patient in the Japanese Oncology Group had a good pathologic response to neoadjuvant chemotherapy suggesting pathology-driven chemotherapy treatment in patients with PLB needs further exploration [5]. Fifteen (68%) patients from the Brazilian institution received neoadjuvant chemotherapy however, no comment was made on statistical significance for overall survival [11]. A recent case report has demonstrated a good clinical and radiological response to denosumab in PLB with osteoclast-like giant cells [17]. Again, the effectiveness of chemotherapy remains difficult to study due to low incidence. To date, chemotherapy use has not been shown to be effective. Wide excision remains the gold standard.

Rate of recurrence ranges from 29-64%, usually occurring at a distant site (lung, most commonly) [2,5,11,12]. Recurrence frequently occurs in the first two years post index surgery. Our patient has a 2 mm noncalcified nodule in her lung that has remained unchanged at her follow up scans. Similarly, a case report from a 46-year-old man who was found to have two 2 mm lesions in both lungs that did not show any progression during the following 16 months [19]. Another case study of a 42-year-old woman with an indeterminant 5 cm lung nodule on her initial scans grew by her 4-month follow up and was accompanied by a new lesion [15]. Both were confirmed as metastases with biopsy and treated with lung resection and adjuvant doxorubicin. She had no systemic or local recurrence at 29 months post index surgery [15]. Mori et al found that resection of local recurrence or distant metastases could significantly improve outcomes [5]. Unfortunately, there is insufficient data to comment further on the presence of indeterminant lung nodules and modification in surveillance or treatment.

Conclusion

This is a unique case of low-grade PLB occurring in the proximal fibula presenting with pain. It typically presents as an osteolytic lesion on plain films, though can be sclerotic in the spine. Due to the rare nature of this disease, the use of chemotherapy, denosumab, or other agents cannot be fully supported or rejected. Larger case series and meta-analysis of accumulating literature are needed to better understand and treat PLB.

Clinical Message

This is a rare case report of a low-grade primary leiomyosarcoma of the fibula that further elucidates the demographic characteristics, presentation, microscopic and immunohistochemical findings, management, and prognosis. Although PLB is rare, healthy patients complaining of localized pain and no constitutional symptoms should receive imaging to rule-out this aggressive sarcoma.

Consent: The patient has given their informed consent for the writing of this case report.

Competing Interests: The authors declare that we have no competing interests to report.

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