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Case Report

Pleomorphic Liposarcoma with Metastasis to the Lung and Bone. Report of a case with Uncommon Clinical Presentation and Review of the Literature

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Abstract

Pleomorphic liposarcoma (PLS) is a high-grade sarcoma due to its high rate of recurrence and metastasis [1]. It accounts for only 5% to 15% of all liposarcomas [2]. PLS is most commonly located in the deep soft tissues of the extremities and retroperitoneum [1,3,4] and presents as a painless mass in middle aged and elderly adults [5]. One of the most characteristic features in diagnosis of PLS is the presence of pleomorphic lipoblasts [6]. Typically, sarcomatous tumors metastasize to the lungs [1], and rarely to the bone. This case report describes a 44-year-old male who presented with lung masses as well as masses infiltrating multiple rib bones. The histological and immunohistochemistry profile of these lesions was consistent with metastatic pleomorphic liposarcoma, originating in the thigh, that had been resected 3 years prior to current presentation. The reporting of this case aims to increase awareness of pleomorphic liposarcoma's ability to metastasize, albeit rare, to the bone while also highlighting the usefulness of histology and immunohistochemistry to identify metastatic lesions of pleomorphic liposarcoma.

Keywords: Pleomorphic, sarcoma, metastasis, bone, malignant

ABBREVIATION

PLS: Pleomorphic liposarcoma, **FNA**: Fine needle aspiration, **MFH**: malignant fibrous histiocytoma, **PFS**: progression free survival, **DDLPS**: Dedifferentiated liposarcoma

INTRODUCTION

Liposarcoma is a rare cancer that has high rates of recurrence and metastasis [7]. This tumor has 3 subtypes that exhibit varying clinicopathological and molecular characteristics: well-differentiated/dedifferentiated liposarcoma, myxoid/round-cell liposarcoma, and pleomorphic liposarcoma [8]. The pleomorphic subtype accounts for approximately 5% to 15% of all liposarcomas [2]. It is known for its aggressive course and is highly resistant to conventional treatments [4,9]. PLS is most often found in the deep soft tissues of the extremities and retroperitoneum [1,3,4]. It is typically found incidentally during physical examination or as a painless mass in middle aged and elderly adults [5]. The differential diagnosis of this tumor can include renal cell and adrenal cortical carcinoma, epithelioid sarcoma and epithelioid leiomyosarcoma [1], dedifferentiated liposarcoma [10], and pleomorphic lipoma [1]. Identification of histological features and the use of immunohistochemistry play a pivotal role in differentiating PLS from its malignant counterparts often included within the differential diagnosis. Typical treatment consists of surgical resection [7] and in some cases, chemotherapy, and radiotherapy [11]. However, PLS is classified as a high-grade sarcoma due to a high rate of recurrence and metastasis [1]. As this tumor is a sarcoma, the most common location for metastasis is the lung [1]. We report an uncommon case of pleomorphic liposarcoma of the thigh that metastasized to the lung and interestingly, rib bones. The reporting of this case aims to increase awareness of PLS's potential, albeit rare, to metastasize to the bone. A review of the literature is included that focuses on histological and morphological features, differential diagnoses, and optimal treatment regimens for pleomorphic liposarcoma.

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CASE PRESENTATION

A 44-year-old man presented with recent dyspnea and abdominal pain. Imaging studies revealed three infiltrating right lung masses consistent with malignant neoplasm. In addition, a PET scan showed increased uptake at the left 8th rib with large mass formation. The clinical diagnosis was to rule out metastatic disease from unknown primary. Detailed history was obtained, and the patient reported a history of a large 13 cm right groin pleomorphic liposarcoma, surgically removed two years prior to current presentation. Surgical excision margins of prior sarcoma were multifocally involved by tumor and patient received post-operative radiation and chemotherapy.

Work up of current presentation included Fine needle Aspiration (FNA) cytology preparation performed on one of the lung masses as well as the rib mass and adequate material was obtained including sufficient cellblock preparation for immunohistochemistry studies. Both sites showed similar findings and a diagnosis of metastatic pleomorphic liposarcoma was rendered.

Surgical wedge resection of the lung masses as well as surgical debulking removal of the rib mass were performed. Evaluation of the surgical margins of resection was not possible due to the moderate infiltrating nature of the tumor in the lung and in the rib bone. The largest lung mass measured 3.5 cm and the infiltrating rib mass measured 6.5 cm. The excised tumor masses were multinodular, white yellow, with areas of hemorrhage and necrosis. The rib mass showed a high-grade sarcoma infiltrating the rib bone (**Figure 1A**). The histomorphology of the tumor showed pleomorphic spindle cells of high-grade sarcoma with scattered highly atypical lipoblasts. Focal typical liposarcomatous areas were identified, but there was no evidence of well differentiated liposarcoma. High grade bizarre pleomorphic cells were present in more than 80% of the tumor mass with dominant malignant fibrous histiocytoma (MFH)-like pattern and abundant multinucleated giant cells. Mitotic activity was easily identified with more than 20 mitosis/10 HPF in addition to extensive necrosis and vascular invasion (**Figure 1 B-C-D-E-F**). The tumor cells were positive for Vimentin, S-100 and focally for SMA. Tumor cells were negative for CD45, CD30, Cytokeratin Cam 5.2, desmin, and myogenin. The surgical excision diagnosis was in support of the cytology sampling diagnosis of metastatic pleomorphic liposarcoma.

Patient received post-operative radiation and chemotherapy with mild improvement but expired four months later as a result of extensive lung and bone metastasis.

DISCUSSION

Liposarcomas are malignant neoplasms that are categorized into three main groups depending on their unique clinicopathologic and cytogenetic features: well-differentiated/ dedifferentiated liposarcoma, myxoid/round cell liposarcoma, and pleomorphic liposarcoma [12,13]. Pleomorphic liposarcoma (PLS) is the rarest subtype and is characterized by the presence of pleomorphic lipoblasts [14]. It accounts for merely 5% of all liposarcomas [4] and up to 20% of pleomorphic sarcomas [15].

PLS typically affects middle aged and elderly adults but have rarely been reported in young adults and children [5]. A review of the literature done by Wang et al. found that PLS has a slight male predominance (1:1.35) [6]. It commonly arises in the deep soft tissues of the extremities and retroperitoneum [1,3,4] and in rare instances can involve the subcutaneous adipose tissue [16]. Approximately 30-40% of PLS cases originate in the thigh [3]. The clinical presentation of PLS is broad with most patients presenting with a painless mass, or the mass is incidentally found during physical examination [6].

PLS is referred to as a high-grade sarcoma due to its high rate of recurrence and metastasis [1]. As this tumor is a sarcoma, the most common location for metastasis is the lung [1]. A report by Mentzel et al., of 24 cases of PLS with follow up information, reported 5 of 24 patients had local recurrence and 7 developed metastatic disease [17]. In addition, 38% of the patients suffered mortality due to their PLS [17]. Another paper analyzed a total of 63 cases of PLS and found that of the 32 metastatic events, only

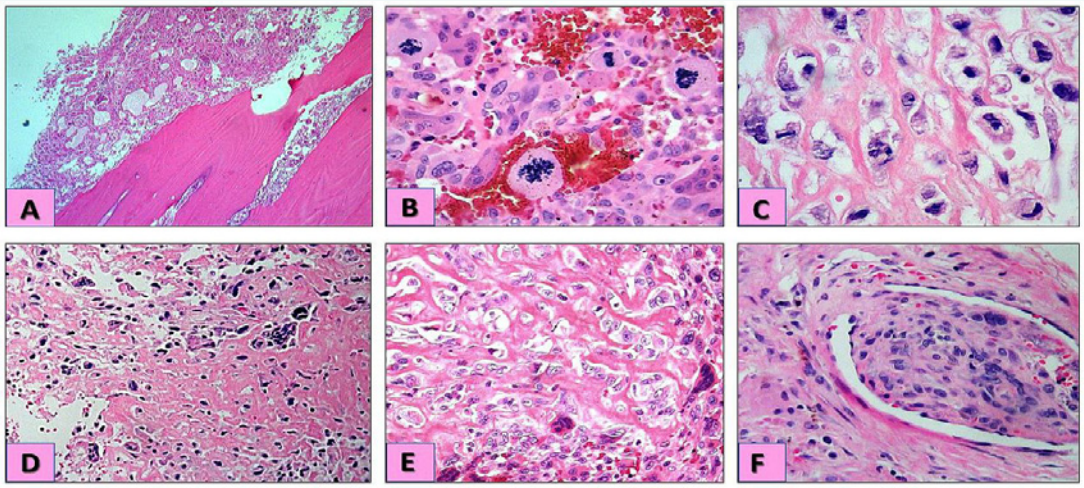

Figure 1 Microscopic description of the bone and lung tumors.
A: Tumor masses infiltrating the rib bone (H&E stain X20).
B: Pleomorphic bizarre tumor cells with increased abnormal mitosis (H&E stain X60).
C: Pleomorphic lipoblasts infiltrating fibrocollagenous tissue, high power (H&E stain X60).
D: Tumor mass showing extensive necrosis (H&E stain X20).
E: Pleomorphic lipoblasts infiltrating fibrocollagenous tissue, medium power (H&E stain X40).
F: Vascular invasion by tumor cells (H&E stain X40).

three were found in the bone [3]. A study done by Ghadimi et al. found that recurrent disease and positive microscopic margins were significant prognostic indicators [9]. Additionally, the presence of older age, central tumor location, tumor size >10cm, tumor necrosis, high mitotic rate and epithelioid morphology were also found to be prognostically significant [9]. PLS has a relatively poor prognosis as the 5-year survival ranges from 29% to 57% and the median interval to death due to PLS is 6 to 30 months [4]. A clinicopathologic analysis by Hornick et al. found that PLS occurrence on the extremities, tumor size <10cm, and mitoses fewer than 10 per 10 HPF are correlated with a more favorable prognosis [4]. It has also been found that subcutaneous PLSs have a much more favorable outcome compared to deep sited tumors [18]. PLS tumors located in the limbs typically have a better local-recurrence free survival compared to truncal tumors or those in limb girdles due to the fact that they are generally easier to remove with tumor free margins compared to proximal lesions [3].

To diagnose PLS, pleomorphic lipoblasts must be present [6]. It is important to note that the prevalence of multi-vacuolated bizarre lipoblasts may vary on a case-by-case basis and these lipoblasts may sometimes congregate into areas within the tumor proving to be a diagnostic challenge [6]. An analysis of 63 cases of PLS found that 32% of cases demonstrated focal adipocytic differentiation, restricted to scattered lipoblasts which only presented as <10% of the tumor [3]. If the pleomorphic lipoblasts are not identified due to lack of close examination or sufficient sample size, PLS may be misdiagnosed as another type of soft tissue sarcoma [6]. The analysis by Gebhard et al. found that 41% of PLS were initially misdiagnosed, most commonly as malignant fibrous histiocytoma (MFH) due to the lack of identification of scarce lipoblasts in the PLS tumor tissue [3]. This highlights the importance of the identification of lipoblasts and significance of adequate tumor sampling in achieving successful diagnosis of PLS [3].

A significant number of PLS cases resemble malignant fibrous histiocytoma-like (MFH) tumors by presence of pleomorphic spindled cells with few multinucleated giant cells arranged into a storiform pattern [1]. In some PLS tumors, only focal groups of lipoblasts were present, highlighting the importance of adequate sampling of the tumor to approximate lipoblastic differentiation [1]. To a lesser extent, some PLS tumors are mainly composed of epithelioid cells [1]. This subtype of PLS is characterized by sheets of epithelioid cells with round nuclei, occasional prominent nucleoli, and cytoplasm that can range from vacuolated to eosinophilic [1]. A subset of these tumors are arranged around a hemangiopericytoma-like vasculature [1].

The differential diagnosis of PLS is dependent upon the predominant histologic pattern of the tumor. The epithelioid pattern is often mistaken for a carcinoma, notably renal cell and adrenal cortical carcinoma [1]. This is explained by the statistic that focal immunoreactivity for cytokeratin occurs in up to 50% of epithelioid PLS [19]. The main differentiating factor between epithelioid PLS and renal cell carcinoma is the fact that RCC expresses epithelial membrane antigen while PLS does not [1]. In addition, epithelioid PLS cells exhibit large lipid-filled vacuoles but cells in RCC demonstrate multiple small intracytoplasmic lipid droplets [1]. On the other hand, adrenal cortical carcinoma has no immunoreactivity for cytokeratin or epithelial membrane antigen [1]. It can be differentiated from PLS by its distinctive fine lipid droplets in comparison to the large lipid-filled vacuoles seen in PLS [1]. Other sarcomas that display epithelioid features are considered in the differential diagnosis including epithelioid sarcoma and epithelioid leiomyosarcoma [1]. However, cytokeratin, CD34, epithelial membrane antigen, and muscle cell markers are used to differentiate these from PLS [1]. A large subset of PLS have similarities to other high-grade pleomorphic sarcomas including pleomorphic leiomyosarcoma, pleomorphic rhabdomyosarcoma, pleomorphic malignant peripheral nerve sheath tumor and MFH [1]. The differentiation of these types of pleomorphic sarcomas requires features visualized by light-microscopy [1] and by immunohistochemistry studies.

Furthermore, dedifferentiated liposarcoma (DDLPS) may in rare instances mimic PLS by lipogenic differentiation [10]. A study by Mariño-Enríquez et al. elucidated that the presence of significant pleomorphism and highly atypical lipoblasts suggests diagnosis of PLS [10]. In addition, immunohistochemistry can be used to diagnose DDLPS by MDM2 and CDK4 expression via FNA cytology with adequate cellblock preparation [10]. The use of clinicoradiologic correlation, extensive sampling and review of the patient's history often leads to evidence of dedifferentiated liposarcoma evolving from well-differentiated liposarcoma [4].

Pleomorphic lipoma is the only benign lesion that shares similar features to PLS. However, pleomorphic lipomas typically are found in middle aged males as well-circumscribed subcutaneous mass on the posterior neck, back or shoulders [17]. From a histological standpoint, pleomorphic lipoma is composed of a mixture of adipocytes and atypical hyperchromatic cells such as multinucleated floret-like giant cells and collagen bundles [1]. Pleomorphic lipomas also have strong immunoreactivity for CD34 marker [20].

Complete surgical resection of the tumor is the only definitive treatment [7]. The use of cytotoxic chemotherapy and radiation remains debatable for treatment for metastatic or unresectable liposarcoma [11]. A case of PLS that failed chemotherapy demonstrated that treatment with Apatinib achieved a 3-month progression free survival (PFS) suggesting its use in advanced cases of PLS [7]. The poor prognosis of PLS despite treatment highlights the need for advancements in therapeutic approaches. The case we present is unique in that a pleomorphic liposarcoma metastasized to the bone, which is atypical for sarcomas as they often metastasize to lung tissue. Specifically, it highlights the usefulness of histology and immunohistochemistry in differentiating mimics of PLS and tissue sites of origin of metastatic lesions. Further studies must focus on generating a precise immunoreactivity as well as histomorphological profile of PLS.

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