Metastatic Undifferentiated Pleomorphic Sarcoma Causing Intraoperative Stroke

Reed Spaulding IV, Theodoros Koumoundouros, and Joseph C. Parker Jr.

University of Louisville Hospital, Louisville, KY, USA

Abstract. Malignant Fibrous Histiocytoma was historically the most commonly diagnosed soft tissue sarcoma of adults. In 2002, the World Health Organization declassified malignant fibrous histiocytoma as a formal diagnostic entity. They recommended renaming the disease “Pleomorphic Undifferentiated Sarcoma”. Current thoughts about the origin of this tumor are being debated. We report a case of a dedifferentiated liposarcoma that metastasized to the lung within one year. The histologic morphology of the metastasis was more aggressive than the primary lesion, and was consistent with a pleomorphic undifferentiated sarcoma. Following surgical resection of the metastatic pulmonary lesion, the patient never fully regained consciousness. He expired the day following his surgery. At autopsy, the patient was found to have died from a massive hemorrhagic stroke involving almost the entire left cerebrum. Tumor emboli from the pulmonary metastasis were seen in the left middle cerebral artery, causing the cerebral infarct. The embolic lesion was consistent with a pleomorphic undifferentiated sarcoma. This case illustrates the evolution that soft tissue sarcomas can undergo as they metastasize and become increasingly undifferentiated, and confirms the surgical risk of resecting such lesions.

Key words: Pleomorphic undifferentiated sarcoma, malignant fibrous histiocytoma, embolus, liposarcoma

Introduction

First described in 1961, MFH was once the most commonly diagnosed soft tissue sarcoma in adults [1]. As the disease entity became further characterized, it was subdivided into five morphologic variants: storiform-pleomorphic, myxoid, giant cell, inflammatory, and angiomatoid [1,2]. Evidence suggesting that MFH represented a final common pathway in sarcomas as they progress towards undifferentiation prompted the World Health Organization (WHO) to declassify MFH as a formal diagnostic entity in 2002 [1,3].

The etiology of UPS is currently being debated, with two schools of thought predominating. The most widely accepted idea is that UPS represents a morphologic pattern that is common to a number of sarcomas as they become increasingly undifferentiated [1,4-6]. Recent studies using comparative genomic hybridization and gene expression arrays support this conclusion [7,8]. A competing idea is that UPS results from the transformation of mesenchymal stem cells (MSCs), not the loss of differentiation markers from previously differentiated tumors [4]. Data from recent studies indicates that different subtypes of sarcomas are derived from MSCs at different times along their path to becoming a mature lineage [9,10].

Case Presentation

A previously healthy 52 year old Caucasian male developed an enlarging mass in his right axilla and shoulder region which was resected in December 2009. A 12.0 X 11.0 X 8.0 cm, circumscribed, mildly lobulated tan-brown mass was removed. Histologic sectioning of the tumor revealed a dedifferentiated liposarcoma (Figure 1), with characteristic well-differentiated areas in close proximity to dedifferentiated areas. The patient received 33 treatments of external beam radiation to the area following the procedure. One year later, in December 2010, the patient presented to a nearby...
emergency department with presumed left sided community-acquired pneumonia and acute mild hypoxic respiratory failure. CT of the chest revealed a 6.0 X 6.0 X 4.0 cm left hilar lung mass. The patient underwent a left thoracotomy with a left pneumonectomy, which revealed the previously described mass extending into the left main pulmonary artery and left superior pulmonary vein, as well as the left mainstem bronchus. The patient tolerated the procedure well. He was slow to awaken, but hemodynamically stable and was transferred to the post-operative care unit. Histologic sectioning of the metastatic pulmonary tumor revealed a prominent spindle cell population (Figure 2). The morphology was noted to be of higher grade than the primary specimen, but was diagnosed as consistent with the patient’s known diagnosis of dedifferentiated liposarcoma.

Following the left pneumonectomy, the patient never fully regained consciousness. A subsequent CT of the head revealed multiple areas of reduced gray-white differentiation compatible with multiple early acute infarcts, primarily involving the left cerebral hemisphere. MRI revealed extensive acute infarcts within the brain parenchyma involving the left middle cerebral artery distribution including almost the entire left cerebrum. The patient’s respiratory status continued to decline, he developed paroxysmal supraventricular tachycardia, and became completely unresponsive. The patient expired the day after the procedure. A full autopsy was performed, and gross examination of the brain revealed tumor embolus in the left middle cerebral artery. Histology of the tumor embolus was similar in character to the previous metastatic resection, with a population of high grade, spindled, pleomorphic cells (Figure 3). Due to the high grade morphology and lack of adipocytic component, as well as the immunostains performed, the tumor embolus was diagnosed as malignant fibrous histiocytoma (MFH), now referred to as undifferentiated pleomorphic sarcoma (UPS).

Discussion

We report a case of a primary dedifferentiated liposarcoma that, within one year, metastasized to the patient’s right lung. Histologic sections of the metastatic lesion were consistent with UPS, with no observable lipogenic component. After resection of the lung lesion, the patient developed clinical signs and symptoms of an embolic stroke and histologic sections of the occluded left middle cerebral artery revealed that the embolus was consistent with the previously resected metastatic lesion.

Figure 1. Dedifferentiated liposarcoma. (A) Low power view showing well differentiated and dedifferentiated components in close proximity. (B) Higher power views, showing the well differentiated component, and (C) more aggressive, pleomorphic appearing dedifferentiated component.
Perioperative stroke caused by arterial tumor embolism of UPS has been previously reported [11]. In that case, both the primary tumor and the metastatic lung lesion were both histologically consistent with UPS. Nicolas M, et al. documented that lung metastases from dedifferentiated liposarcoma are often nonlipogenic [12]. Out of eight patients with a primary diagnosis of dedifferentiated liposarcoma who subsequently developed pulmonary metastases, the histomorphologic features in three cases displayed “pleomorphic cells with admixed bizarre giant cells and multinucleated cells” consistent with UPS [12]. In that study, all patients developed pulmonary metastases involving the left lung, with some cases involving bilateral lungs.

Concerns about the over diagnosis and etiology of MFH began before the turn of the last century. One large study involved reassessing 159 tumors diagnosed as pleomorphic sarcomas from a morphological, immunohistochemical, and ultra structural standpoint [6]. Of these, “97 cases (63%) proved to be specific sarcomas other than MFH, 20 proved to be nonmesenchymal neoplasms, and 42 were unclassifiable (of which 21 were either small biopsies or subtotally necrotic). Only 13% of these cases were eligible for consideration as MFH, but these showed no reproducible histological differences from the other tumors studied, nor was this group morphologically consistent” [6].

In 2002, the World Health Organization (WHO) declassified MFH as a formal diagnostic entity in light of increasing evidence that these lesions represented a final common pathway in sarcomas as they progressed towards undifferentiation.[1,3]. A number of changes occurred to the WHO classification of the morphologic variants of MFH. These changes in the classification scheme are summarized below [3,4]:

A) Removal of the myxoid and angiomatoid variants of MFH, with these entities being reclassified as “myxofibrosarcoma” and “angiomatoid fibrous histiocytoma,” respectively.

B) Renaming of the storiform-pleomorphic variant of MFH to “Undifferentiated high-grade pleomorphic sarcoma” (UPS), and reserving this diagnosis for cases in which no line of differentiation can be identified.

C) Reserving the giant cell and inflammatory variants to those cases in which no evidence of differentiation can be identified, with the new names “UPS with Giant cells” and “UPS with prominent inflammation”.

Subsequent comparative genomic hybridization analysis has shown that the chromosome imbalances encountered in a series of 22 cases of MFH were very similar to those observed in a series of 9 pleomorphic liposarcomas, suggesting a close relationship between the two entities [8]. Similarly, a recent study of 160 soft tissue sarcomas with complex genomics (i.e. multiple genetic alterations) including myxofibrosarcomas, pleomorphic liposarcomas/rhabdomyosarcomas, and undifferentiated pleomorphic sarcomas found common alterations of certain genes, including RB1, PTEN, and DKK1 (a WNT pathway inhibitor) [7].

Recently, more interest has been given to the idea of UPS arising from MSCs as evidenced by a recent publication studying gene expression during in vitro differentiation of human mesenchymal stem cells into adipose tissue [9]. They compared liposarcomas to their corresponding adipose cells as they matured along their lineage, and found a “group of genes overexpressed in liposarcomas that indicate the stage of differentiation arrest” as well as a “distinct set of genes overexpressed in liposarcomas that are not found in the corresponding stage.
Metastatic Undifferentiated Pleomorphic Sarcoma Causing Intraoperative Stroke

of differentiation” [9]. They postulated that a quantitative score of developmental maturity could thus be assigned to these tumors, and that tumor stem cells can develop at different times during adipocyte maturation [9].

Our case supports the concept that UPS is a morphologic pattern common to various sarcomas as they become increasingly undifferentiated, as evidenced by the change in morphology upon metastasis; however, it has become clear that answering the question of how UPS comes to exist cannot be answered by morphology alone. Evaluation of metastatic myxoid liposarcoma to the lung is greatly confounded by therapy-related changes, making it difficult to appreciate the true cellularity and cytologic appearance of the neoplastic cells [12]. Is a similar misleading phenomenon occurring in our case, where previous radiation has induced cellular change that is morphologically consistent with UPS?

Conclusion

Answering the questions that surround the origin of UPS will continue to involve a combination of morphologic, immunohistochemical, and molecular genetic analysis. Our case confirms the surgical risk involved in resection of these lesions, and gives further justification for the declassification of MFH as a formal diagnostic entity by the WHO in 2002. While our case supports the concept that UPS is a product of progressive undifferentiation of sarcomas that were previously able to be characterized, the impact of post-operative radiation may have played a causative role in the more aggressive-appearing morphology of the pulmonary metastasis. As molecular analysis becomes more integral in anatomic pathology as a whole, future management of these neoplasms will increasingly rely on characterizing their cell of origin.

Acknowledgements

We would like to thank Dr. Timothy Matthews and Dr. George Kunz who were involved with the autopsy of this patient.

References