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Liposarcoma of the left hemithorax and implications of MDM2

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Case Study

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Abstract

Background: Use of molecular information to guide clinical management of thoracic liposarcoma following resection.
Case presentation: We present a case of a large liposarcoma of the left hemithorax. Initial biopsy consistent with lipoma however following resection pathology showed well-differentiated liposarcoma. Clinical data and molecular information including MDM2 from the tumour were employed in decision making regarding subsequent adjuvant radiation therapy versus close observation.
Conclusion: Improved molecular characterisation has increased the precision of histological diagnoses and prediction of outcomes for many cancers. These may continue to help guide and strengthen clinical decision making and recommendations as they pertain to adjuvant therapy versus observation in the case of this patient.

Case Report

A forty-eight-year-old Caucasian male presented to urgent care complaining of respiratory symptoms that began several days prior and included ear pain and fullness with chest congestion. Prior to this, he was completely asymptomatic and had no known medical issues. Auscultation revealed no breath sounds on his left side which prompted a chest X-ray (Figure 1) which revealed near complete white-out of the left hemithorax. The patient was sent immediately to the emergency department and underwent computed tomography (CT) of the chest (Figure 2) which showed a fat-containing mass measuring over 40 cm in the left hemithorax with compression of the mediastinum. A subsequent magnetic resonance imaging of the chest showed no evidence of invasion of the mass into the chest wall, diaphragm or mediastinum.

The patient then underwent a CT-guided biopsy of the left thoracic mass. Pathology showed mature adipose tissue consistent with lipoma. A staging CT of the abdomen and pelvis showed no evidence of metastatic disease. Thoracic surgery was consulted, and the following week, the patient underwent a thoracotomy and resection of his left chest mass. The final pathology of the resected mass was determined to be a Stage IIB (pT2bNXMX) well-differentiated liposarcoma. All surgical margins were negative. Fluorescence in situ hybridisation analysis using the murine double minute 2 (MDM2)-specific probe was applied to 400 interphase nuclei. It revealed a polysomy (3–5 copies) of MDM2 in 140/400 (35%) cells. No other genomic aberrations were detected.

Management

After recovering from his surgery, the patient was seen by both medical oncology and radiation oncology. A multidisciplinary discussion took place both in clinic and at tumour board evaluating the need for adjuvant treatment. The final recommendation was for a positron emission tomography (PET) scan to exclude metastatic disease and ongoing active surveillance thereafter. This was based on the presence of negative margins, well-differentiated appearing cells and positive MDM2, lack of consensus guidelines for adjuvant radiation for completely resected well-differentiated liposarcoma and the potential risk of pulmonary toxicity secondary to radiotherapy that would include the entire left thorax in a young and otherwise healthy male.

The post-operative PET scan displayed a mild hypermetabolic region along the inferior aspect of the pleura (Standardized uptake value (SUV) 2·5) and in the chest wall posteriorly at the surgical incision (SUV 5). There was no corresponding fatty mass at those locations or visible residual tumour. No hypermetabolic adenopathy or hypermetabolic distant metastases were appreciated. The patient was recently seen in clinic and is doing well with no sequelae from his disease now 3 years from his surgery. Follow-up imaging has continued to remain negative for presence of metastatic disease or recurrence.

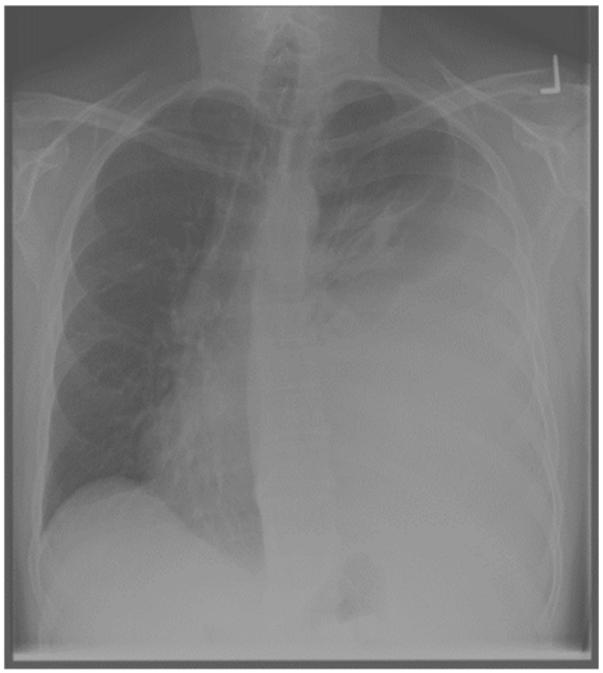

Figure 1. X-ray of the chest – AP view.

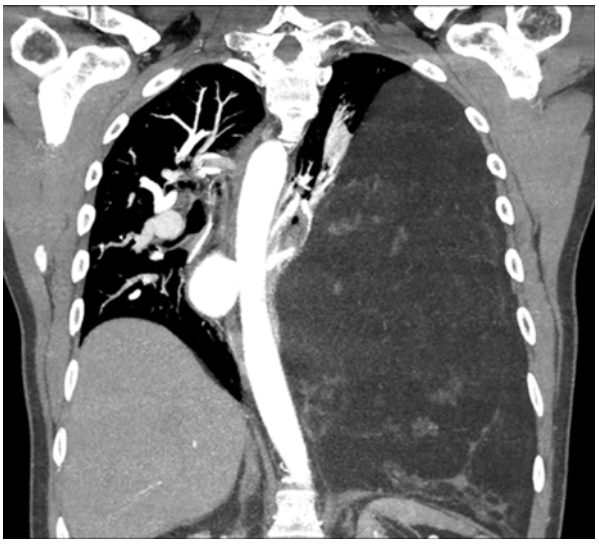

Figure 2. CT of the chest – coronal view.

Discussion

Adipocytic neoplasms represent the most common soft tissue tumour, which includes both lipomas and liposarcomas. Well-differentiated liposarcoma (WDL) and dedifferentiated liposarcoma (DDL) make up the majority of liposarcomas and are thought to represent different stages of progression along the same disease axis.[1] Liposarcoma is graded based on histological appearance and differentiation, mitotic count and presence of tumour necrosis. Higher grade tumours are more likely to be infiltrative and to metastasise and thus may benefit from adjuvant therapy following surgery. Therefore, the ability to predict increased aggressiveness in cases of liposarcoma remains important to clinical decision-making.

Within the last 10–15 years, there has been an increase in cytogenetic and molecular genetic information of various neoplasms including liposarcoma. Recently, cell cycle regulator genes have attracted attention for both diagnostic and prognostic assessment of sarcomas. One of these is the MDM2 gene found in the chromosomal 12q13-15 region in some sarcomas including liposarcoma.[2] The MDM2 gene encodes an important regulator for p53 by directly binding and subsequently causing a loss of function.[3] Use of MDM2 amplification status has become the gold standard to differentiate WDL versus lipoma.[4] This may be helpful in several problematic situations including 'lipomas' greater than 10 cm, those found in the abdominal/retroperitoneal area or in cases where the initial biopsy is inconsistent with the clinical or radiological features as in the case presented above.

Several studies have suggested that MDM2 amplification occurs as an isolated event in tumourigenesis of liposarcoma rather than a continuum between lipoma and well-differentiated liposarcoma.[5] This is corroborated by findings of MDM2 overexpression in both WDL and DDL but not in lipoma.[6] While the presence or absence of MDM2 amplification has been shown to provide some clarity in distinguishing malignant from benign adipocytic neoplasms, the role of MDM2 in WDL versus DDL is less clear. This becomes important as 15–20% of DDL cases may metastasise compared to WDL which recurs locally.[7]

A recent study looked at copy numbers associated with MDM2 amplification and their ratio to a standard centromeric probe in 46 cases of liposarcoma. WDL and DDL samples showed a high degree of MDM2 amplification in the majority of the cases tested. In addition, DDL had both higher copy numbers per cell as well as the ratio of MDM2 to the centromeric probe when compared to WDL.[8] The results suggest that the degree of amplification of MDM2 may be related to identification and/or risk of progression to DDL, which in turn might increase the likelihood of metastatic disease. The disease course of DDL is very different to WDL,[9] and the catering of treatment modalities has been explored.[10] Prediction of aggressiveness in WDL/DDL samples using MDM2 amplification may provide additional clinical direction in regard to adjuvant therapy.

Conclusion

The presence of MDM2 amplification has been used in delineating WDL/DDL from other lipomatous tumours. Further investigation of MDM2 to distinguish WDL from DDL has shown some interesting results, especially when the initial treatment and overall outcome can be quite dissimilar. Improved molecular characterisation has increased the precision of histological diagnoses and prediction of outcomes for many cancers. These may continue to help guide and strengthen clinical decision-making and recommendations as they pertain to adjuvant therapy versus observation in the case of this patient.

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