Markedly pleomorphic epithelioid cells with high mitotic activity, giant cell formation, very large atypical nuclei, multiple nucleoli and abundant cytoplasm characterize ‘monster’ cells and may indicate aggressive tumor behavior. Very rare reports of melanomas comprised of ‘monster cells’ or cells with comparable histomorphological features, found in tissue samples from skin, lymph nodes, CNS, oral cavity and ileum have been published in the literature. This case is the first such description in the lung, and it is characterized with a battery of immunohistochemical stains; BRAF mutation status was negative, and fluorescence in situ hybridization analysis revealed increased copy number gains in 11q (cyclin D1), which is associated with poor prognosis in melanoma. The presence of monster cells in melanoma was associated with aggressive behavior in the reported patient.

Keywords: cyclin d1, FISH, melanoma, metastasis, monster cells


The term ‘monster cells’ refers to cells with significantly enlarged nuclei that are pleomorphic in nature, with large atypical nuclei, multiple nucleoli and abundant cytoplasm. The first report of ‘monster cells’ in the literature was by Tamada and Ackerman in 1987, who described these cells in the early, histiocytic stage of dermatofibroma and described only rare mitotic figures that were neither numerous nor atypical.1 Monster cells have subsequently been reported in case reports of dermatofibroma studies exploring immunohistochemical features.2–4 The use of the term ‘monster cells’ has since been used to describe findings in other cutaneous proliferations including malignancies such as basaloid squamous cell carcinoma,5 basal cell carcinoma6 and melanoma; in contrast to the original descriptor, monster cells in these malignancies show prominent mitotic activity. The term was first utilized to characterize cells in melanomas in the identification of 13 cases of melanoma with monster cells in a case series by Boyd et al. in 2005.7 Previously, terms such as ‘pleomorphic’ or ‘anaplastic’ signified melanomas with cells containing large, bizarre and hyperchromatic nuclei with atypical mitotic figures,8 which typically stain positively with immunohistochemical markers of melanoma such as S-100, NKI-C3 and HMB-45. Such cases have been described from melanoma tissue samples from skin and lymph nodes,7 central nervous system,8,9 mucous membranes of the head and neck10–12 and ileum.13 Melanomas with monster cells have been associated with aggressive behavior; in fact Sidhu and Sidhu proposed naming these tumors ‘monstrocellular melanomas’.13 Herein we report the first case of melanoma with monster cells in the lung, and characterize this tumor with a battery of immunohistochemical stains, and BRAF genotyping. The aggressive clinical behavior prompted our analysis of the tumor
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with respect to genetic copy number gains that are associated with poor prognosis in melanoma.\textsuperscript{14}

Case report

A 61-year-old woman presented to the hospital with 3 weeks of progressive shortness of breath, and was found to have a 17-cm left upper lobe lung mass with pleural effusion. A core needle biopsy of the left upper lobe lung lesion was significant for a malignant epithelioid neoplasm with extensive necrosis.

Three days later, a computerized tomography (CT)-guided lung biopsy was performed and revealed a malignant pleomorphic epithelioid neoplasm with extensive necrosis, and immunohistochemistry supported a diagnosis of metastatic melanoma, as described below. Upon physical examination of the patient, no cutaneous melanoma was identified; however, intra-abdominal metastases were discovered by CT imaging. Chemotherapy was initiated with dacarbazine monotherapy while awaiting further characterization of her tumor, but the patient died less than 20 days after presentation from progressive respiratory complications.

Materials and methods

Staining of sections with hematoxylin and eosin and for immunohistochemistry was performed as per the standard laboratory protocol. The following antibodies and dilutions were utilized from Dako Laboratories: ALK-1, 1 : 25; Mib-1 (Ki67), 1 : 100; Cytokeratin MNF116, 1 : 100; Desmin D33, 1 : 50; CD-1a Clone 10, 1 : 50; CD30 BerH2, 1 : 40; MITF D5 clone, 1 : 40; Cytokeratin AE1-3, 1 : 50; LCA (CD-45), 1 : 200; S-100 Protein, 1 : 3200 and HMB-45, 1 : 100 (Dako North America, Carpinteria, CA, USA); and from NeoMarker: DC15 Ab-3 1 : 25 and BCL-1 1 : 10 (NeoMarker, Lab Vision, Fremont, CA, USA). Mutation analysis for BRAF exons 11, 12 and 15 was performed. In summary, tumor from paraffin embedded, formalin fixed tissue was grossly micro-dissected prior to DNA extraction. Genomic DNA was extracted and subjected to polymerase chain reaction-based sequencing of the BRAF gene in three separate reactions for exons 11, 12 and 15 (spanning codon 600), which together comprise greater than 99% of the known activating mutations in BRAF (Quest Diagnostics, Chantilly, VA, USA). Fluorescence in situ hybridization (FISH) analysis and in situ hybridization with a probe targeting 11q13 was performed as previously described.\textsuperscript{14} In summary, the tumor was scanned for areas with chromosomal copy number aberrations in the targeted areas. Areas showing copy number aberrations were enumerated as previously described.\textsuperscript{15}

Results

Histopathologic examination of tissue obtained by CT-guided lung biopsy revealed a malignant neoplasm with nodules of ‘monster cells’, characterized by markedly pleomorphic epithelioid cells with high mitotic activity, giant cell formation, very large atypical nuclei, multiple nucleoli and abundant cytoplasm (Figs. 1 and 2). Multiple clusters of mononuclear inflammatory cells including lymphocytes and histiocytes were noted within and surrounding the tumor deposits. The tumor cells were highlighted by diffuse positive immunohistochemical staining for vimentin, S-100 (Fig. 3), NK1/C3, WT-1, and focally for pan-melanoma marker (comprised of HMB-45, tyrosinase and MART-1). Tumor cells did not stain with Melan A, AE1/AE3, CK 5/6, MOC31, Calretinin, CEA(p), CAM 5.2, TTF-1, CK7, CK20, CD45, CD30 or CD68. CD45 highlighted inflammatory cells and CD68 revealed histiocytes in the sample. In particular, S-100, MiTF (focal; Fig. 3) and CD30 (focal) were positive in the giant/monster cells, and desmin, ALK, LCA, CD1a, MART-1, HMB-45, MNF116 and AE1/AE3 were negative. Taken together, the combination of these unusual histopathologic and immunohistochemical features were most consistent with a diagnosis of melanoma with monster cells. No primary lesion was identified on the patient and the lung mass was consistent with metastasis from an unknown primary site.

Additional studies were carried out after the patient’s death, and further post-mortem analysis of the tissue block was performed to further characterize this malignancy with aggressive clinical behavior, and it also gave the rare findings of monster cells throughout the metastatic melanoma tissue. Cyclin D1 was diffusely positive by immunohistochemistry,
and Ki-67 (MIB-1) showed a high proliferation index (Fig. 3). No mutations in BRAF exon 11, 12 or 15 were detected by mutational analysis. FISH analysis of the formalin-fixed, paraffin-embedded tissue showed copy number gains in 11q (cyclin D1) (Fig. 2).

**Discussion**

The presented case illustrates the first description of the melanoma with monster cells in the lung, and this report characterizes a clinically aggressive tumor that was rapidly fatal. Monster cells in melanoma have been previously associated with aggressive behavior and worse clinical outcomes.\(^{13,16}\) We sought to further characterize this tumor and explore features suggestive of poor outcome.

When Boyd et al. first utilized the term ‘monster cells’ in melanomas, their report described 13 cases (from a review of 99 randomly selected melanoma cases) and found a significant association with nodular subtype, ulceration, depth of invasion and presence of multinucleated giant cells in these tumors.\(^7\) Although the authors were cautious to avoid ascribing prognostic implications to monster cells because of such low sample numbers and lack of long-term evaluation, it is important to note that two of the significantly associated histopathological findings (ulceration and depth of invasion) are associated with higher stage and worse outcomes in melanoma according to the most recent iterations of the American Joint Committee on Cancer and National Comprehensive Cancer Network melanoma guidelines.\(^{17,18}\) The association of monster cells in melanoma with other features of aggressive clinical behavior favors an unfavorable clinical course.

In this case, immunohistochemical staining was utilized to support a diagnosis of melanoma, in addition to providing information about tumor behavior. To explore whether monster cells represent actively proliferating cells, Boyd et al. stained two melanomas with monster cells for MIB-1 and found negative staining of monster cells, with surrounding tumor cell positivity.\(^7\) In the current case, the tumor cells (including monster cells) were strongly and diffusely positive for MIB-1, indicating active proliferation of these cells.

The BRAF mutational analysis has become a frequent test for high-stage melanomas (including
Fig. 3. Immunohistochemistry highlights tumor cells as positive for S-100, MiTF (local), a high proliferation index by Ki-67 (MIB-1) and positive for cyclin D1.

those with unknown primary site), and may indicate whether patients would benefit from a course of mutation-targeted therapy. Analysis of Australian melanoma patients harboring BRAF mutation found association with a younger age at diagnosis and of distant metastasis, suggesting an aggressive clinical course. While the melanoma with monster cells presented in this study did not contain a BRAF mutation, genetic characterization of future similar cases with monster cells may yield useful insights for prognosis and management strategies.

Cyclin D1 amplification is associated with poor prognosis in a number of tumors, such as neuroblastoma, metastatic colorectal carcinoma, estrogen receptor positive breast cancer, nasal type natural killer/T-cell lymphoma, and pancreatic ductal cancers. Recently, homogenous staining regions for cyclin D1 were recently found to be a marker of poor prognosis in melanoma. Of note, cyclin D1 is not uniformly a marker for poor prognosis: it was not found to associate with poor prognosis for periampullary carcinomas and a recent meta-analysis of non-small-cell lung cancer showed cyclin D1 unlikely as a useful prognostic marker for this disease.

In 2009, Pouryazdanparast et al. utilized FISH to show a massive cyclin D1 amplification, with at least 30 gene copies within monster cell nuclei. These authors proposed that the monster cells are uniquely able to tolerate this level of genomic instability, with cyclin D1-mediated proliferation and cell-cycle activation corresponding to aggressive clinical course. Gerami et al. further utilized FISH to identify specific copy number gains in the chromosomal loci for cyclin D1 (11q13) and Myc (8q34) that were significantly associated with metastasis in a study of 97 melanomas. The presented case showed Cyclin D1 positivity by immunohistochemistry, and FISH analysis revealed gains in 11q13, although not nearly at the levels of amplification previously reported. While the presented case does not feature cyclin D1 amplification limited to the monster cells as previously observed, we suggest that these pleomorphic cells occur in association with the high proliferative index, degree of overall cyclin D1 amplification and the clinical finding of aggressive disease.
In summary, we present a case of melanoma with monster cells in the lung, with cyclin D1 copy number gains. We hypothesize that the highly atypical nuclear features with greatly enhanced nuclear size and atypia directly correlate with the severe genomic instability and hence the highly aggressive clinical behavior. The presence of such genomic or morphologic aberrations may portend an unfavorable aggressive clinical course and prompt escalated therapeutic intervention.

References