Metastatic melanoma — a case report of rare cyto-morphologic variant in fine needle aspiration specimen

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Abstract
Melanoma is infamous for its ability to mimic other tumours and metastasise anywhere within the body. Our case, a 67-year-old male patient, presented with an enlarged right axillary lymph node. Fine needle aspiration was performed. Cytological slides showed a rare morphologic variant: mixed spindle cells with nuclear grooves and epithelioid/plasmacytoid cells without macronucleoli. Immunostaining was performed on cell block sections. Tumour cells demonstrated S-100 and Melan-A, and melanoma was diagnosed. Morphologic variants of melanoma can pose a significant challenge to cytological diagnosis, which often requires supplementation using immunocytochemical stains.

Key words: metastatic melanoma, spindle cell, nuclear grooves, fine-needle aspiration, cytology, immunocytochemistry.


Introduction
Melanoma is an aggressive tumour of melanocytes, accounting for approximately 3% of all cancers. Metastatic melanoma with rare morphologic variants poses a cytological diagnostic challenge.

Case report
A 67-year-old male patient presented with an enlarged right axillary lymph node and had no clinical history of previous malignancy. Fine needle aspiration was performed on site by a pathologist. The aspirated material was expelled onto glass slides using a syringe and smeared. One slide was rapidly fixed in 95% alcohol for latterly Papanicolaou (Pap) staining (1). The other slide was air dried for Diff-Quik staining (1) and assessed immediately by the pathologist for specimen adequacy. The remaining aspirated material and the needle rinses were subjected to centrifugation, and the sediment used for cell block preparation by the serum-thrombin method (1). Immunostaining was performed on the cell block sections.

We used EnVision™ detection systems, and peroxidase/DAB methods in an autostainer (BenchMark XT) for the immunostaining. The primary antibodies used were those against CK7 (Dako; Clone OV-TL12/30; 1: 600), CK20 (Dako; Clone Ks20.8; 1:100), TTF1 (Dako;  Clone 8G7G3/1; 1:50), P63 (Leica; Clone 7JUL; 1:25), S-100 (Leica; Clone S1/61/69; 1:800) and Melan-A (Cell Marque; CloneM2.7C10; 1:100).

Results
The aspiration was moderately cellular, containing a mixed population of spindle cells (predominantly) and epithelioid/plasmacytoid cells in dispersed, aggregated groups, or cohesive microtissue fragments with a fascicular arrangement (Figure 1). Tumour cells generally showed moderate nuclear pleomorphism, inconspicuous to multiple prominent small nucleoli, coarse and clumped chromatin, and moderate cytoplasm. Epithelioid cells showed dense cytoplasm and distinct cell borders (Figure 2). Many spindle cells exhibited plump nuclei with prominent longitudinal nuclear grooves and ill-defined cell borders (Figure 3). Scattered bizarre epithelioid cells with very large nuclei and bi-nucleate forms were seen. Occasionally intranuclear inclusions were present. Intracellular melanin in neoplastic cells or background melanin pigmentation were absent.

Figure 1. An aggregated group or cohesive microtissue fragment with a fascicular arrangement (Pap IP. Insert HP)

Figure 2. Epithelioid cells show moderate dense cytoplasm and distinct cell borders (Diff-Quick HP. Insert: a bizarre cell with binuclei. HP, Oil)

Figure 3. Prominent longitudinal nuclear grooves (Pap HP. Insert HP. Oil)
Immunocytochemistry: tumour cells stained positive for S-100 and Melan-A (Figure 4). The cell markers of CK7, CK20, P63 and TTF1 were negative.

![Image](NZ J Med Lab Science 2014)

**Figure 4.** Immunocytochemical stain.  
A. Melan-A positive.  
B. S-100 positive (HP)

**Discussion**

Fine needle aspiration (FNA) is a commonly used, rapid, and minimally invasive procedure (2). Metastatic tumours of unknown origin in lymph node FNA specimens present diagnostic problems. Melanoma may mimic a variety of epithelial and nonepithelial tumors, including poorly differentiated carcinoma, lymphoma, and pleomorphic sarcoma (3, 4). Hence identification of metastatic melanoma with unusual morphology, especially when the lesion lacks melanin pigment, presents an increased cytological diagnostic challenge.

The characteristic cytologic features of conventional melanoma are: high cell-yield, predominant epithelioid/plasmacytoid cells with eccentrically placed nuclei and a dissociated pattern, abundant cytoplasm, cytoplasmic melanin pigments, prominent anisokaryosis, macronucleoli, intra-nuclear cytoplasmic inclusions, and variable numbers of bi- and multinucleated cells. A diagnosis of melanoma can be readily made when these characteristic cytologic features are present.

Our case showed a mixed population of spindle cells (predominantly) and epithelioid/plasmacytoid cells, demonstrating nuclear pleomorphism, coarse and clumped chromatin, variable inconspicuous to multiple prominent small nucleoli, and occasionally bi-nucleated tumour giant cells/bizarre nuclei; and lacks the main cytological features elaborated above of conventional melanoma. Morphologic features, especially in the absence of pigment, are similar to a pleomorphic high-grade sarcoma. Melanoma in which spindle cells predominate has been termed “pseudosarcoma”. Indeed, early twentieth-century pathologists discriminated between “melanocarcinoma” and “melanosarcoma”. Erroneous diagnoses have been reported because the overlap of morphologic features (4, 5).

The longitudinal nuclear grooves and intranuclear cytoplasmic inclusions are typical features of papillary thyroid carcinoma (PTC) (6). In addition to the small nuclei, absence of melanin pigment, and no clinical history of malignancy, such cases are likely to be misdiagnosed as metastatic papillary thyroid carcinoma, though axillary lymph node metastasis from PTC is rare (7).

Nuclear grooves have been described as a cytologic feature in a variety of extrathyroid lesions. When a cytologic specimen demonstrates prominent longitudinal nuclear grooving, a wide range of pathologic lesions should be considered, such as dermatopathic lymphadenopathy. Cytologic smears of dermatopathic lymphadenopathy show large dendritic cells with oval, vesicular, grooved nuclei and moderate amounts of pale cytoplasm. In some cases intranuclear cytoplasmic inclusions can be seen (8). Dermatopathic lymphadenopathy can mimic melanoma, particularly when marked with sinus histiocytosis. Chhieng et al reported a case in which bland spindle melanoma cells metastasised to a lymph node and the FNA sample was initially misdiagnosed as a reactive lymph node with fibrosis (9). Previous studies show the lack of nucleoli and the presence of longitudinal nuclear grooves favour a diagnosis of dermatopathic lymphadenitis (8, 10, 11).

Spindle cell melanoma is a rare morphologic variant of melanoma. Cytomorphologically, spindle cell melanomas demonstrate predominant spindle-shaped melanocytes, prominent cellular cohesion, varying degrees of nuclear atypia, and inconspicuous to small nucleoli (12, 13). Spindle cells with nuclear grooves may also be seen in an unusual variant of spindle cell melanoma, desmoplastic malignant melanoma (12). The relative rarity of this variation often leads to misdiagnosis (9).

In metastatic melanoma, misdiagnosis also occurs when an appropriate clinical history is not available. Knowledge of a previous history of melanoma is helpful to avoid an erroneous interpretation. Generally, there are three categories of melanoma: cutaneous melanoma, mucosal melanoma and ocular (uveal) melanoma. Mucosal melanoma is rare, making up less than 5% of melanoma cases. Uveal melanoma, though rare, often presents with nuclear grooves in its spindle cell type (14). The most common site of metastasis for uveal melanoma is the liver, as there are no lymphatic channels to the uveal tract. Cutaneous melanoma is the most common type of melanoma and usually metastasises to regional lymph nodes. For cases of metastatic melanoma with an unknown primary origin, asking relevant clinical history and checking skin, mucosae and uvea may aid in accurate diagnosis, although the original melanoma may have spontaneously regressed. For our case, the most likely primary site of the melanoma was the regional skin around the right upper limb and axilla.

Immunocytochemistry has proved most practical in the identification of metastatic tumours of unknown origin (15). In general, melanoma tumour cells are about 95% immunoreactive to S-100, including the spindle cell variant. Melan-A is a relatively specific but less sensitive marker for melanomas; about 80% of tumour cells are immunoreactive to Melan-A. However despite its relative specificity, Melan-A is often negative in desmoplastic melanoma and cannot completely replace the use of S-100 for the detection of metastatic melanoma (16). Research shows that none of the nonmelanocytic malignant neoplasms, such as pleomorphic high-grade sarcoma, stained with more than one of the melanoma markers (16, 17). In our case, immunocytochemical staining with S-100 and Melan-A protein were positive with the tumour cells, allowing a definitive diagnosis of metastatic melanoma. At the same time, the cell markers of CK7, CK20, P63 and TTF1 were negative, hence they ruled out papillary thyroid carcinoma and other possible carcinomas, and confirm our diagnosis of melanoma.

**Conclusion**

We have presented a case of metastatic melanoma composed of a mixed population of spindle cells with nuclear grooves, and epithelioid/plasmacytoid cells without macronucleoli, which do not demonstrate the conventional diagnostic cytological features of melanoma. Identification of metastatic melanoma with rare morphologic variants, especially when the lesion lacks melanin pigment and there is no clinical history, presents an increased cytological diagnostic challenge. A definite diagnosis of melanoma can be made only after the use of immunocytochemical stains on cell block sections. Immunocytochemical stains to exclude melanoma should be performed in any case of metastatic malignancy of uncertain lineage.
Acknowledgments
The authors acknowledge Thilanie Purdy for her excellent photographic assistance and information on the primary antibodies for immunostaining.

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