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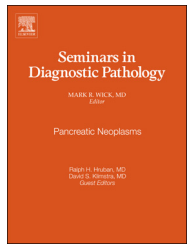

Cytological diagnosis of metastatic malignant melanoma by fine-needle aspiration biopsy

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ABSTRACT

Despite increased surveillance and public awareness, the incidence of melanoma is increasing. Frequently, fine-needle aspiration is employed for the diagnosis of metastatic disease, and aspirated material is used for cytogenetic and molecular studies to guide treatment options. The pairing of a significant diagnosis with the numerous morphologic variants of melanoma can make the cytologic evaluation disquieting. We present selected examples of our experiences and a brief review of the literature to provide cytodiagnostic clues for this malignancy. The clinical history is foremost, although the fine-needle aspiration (FNA) of metastatic melanoma can provide a diagnosis before identification of the primary lesion in up to 20% of cases. If a history of melanoma is assured, negative results in sampling of pulmonary and subcutaneous nodules should be suspected as false negatives. The smearing pattern usually features poorly cohesive cells. Frankly malignant, spindled, and epithelioid cell shapes are most common, and cytoplasmic vacuoles, if sought on Romanowsky-stained specimens, can usually be found. The telltale feature of melanin production, although diagnostic, is only present in 50% of cases. Finally, eccentric placement of nuclei, nucleoli, and nuclear pseudoinclusions are accessory features for the cytologic interpretation of melanoma. Numerous morphologic patterns of melanoma are potentially seen, but a stepwise approach to diagnosis usually produces a successful result.

Melanoma affects over 800,000 individuals in the United States alone. Furthermore, the reported incidence of this tumor is increasing despite decreases in the frequency of other common cancers. Despite improved public awareness, efforts at early detection, and aggressive therapy, morbidity, and mortality figures for melanoma remain staggeringly high.

Understanding of the pathogenesis of melanoma is growing rapidly, and this has resulted in significant advances in its diagnosis and treatment.[1–4] Several genomic alterations have been identified in melanomas and their prevalence may differ by anatomic subtype as well as patient age.[1] *BRAF* mutations are of special importance because of their relatively high prevalence in melanoma. Most analyses have shown that at least 40% of melanomas harbor activating *BRAF* mutations; among them, the most common involves substitution for a valine residue by glutamine at codon 600 (V600E), or, much less frequently, replacement of valine by lysine (V600K).[5] The identification of these aberrations has a role in the diagnosis, prognosis, and treatment of melanoma. Pharmaceutical inhibitors to key enzymes in the *BRAF*-stimulated MAPK gene

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pathway are now part of clinical trials and the results are promising.[3,5,6]

The diagnosis of primary, superficially located melanocytic lesions is usually made with tissue samples that are obtained by punch biopsy, shave biopsy, or elliptical excision. Fine-needle aspiration (FNA) has a very limited role in the evaluation of primary lesions, except in rare and unusual situations. However, the recognition of melanoma has great importance in the setting where FNAs are performed on patients who have a previous history of melanoma and are suspected of having metastatic disease. Because the FNA procedure is rapid, safe, and relatively inexpensive, it has become a principal diagnostic tool for the assessment of possible metastatic disease in lymph nodes and deep visceral organs. In the past 5 years, almost all cases of metastatic melanoma were diagnosed by FNA, with or without concurrent core biopsies, at our institution. Several studies have shown that FNA performs well in the diagnosis of metastatic melanoma, with an estimated sensitivity and specificity of 97% and 99%, respectively.[7–10]

In addition to the evaluation of metastatic disease in sites that are remote from the primary lesion, other studies have been made of "sentinel" lymph node sampling by FNA. A well-designed and performed analysis using both *invivo* and *exvivo* aspirations showed a specificity of 100% but a lackluster sensitivity of 59% in this specific setting.[11] Furthermore, data from that study indicated that high-quality DNA can be extracted from tumor cells on FNA slides, especially those stained with Diff-Quik, for mutational analysis.[12] That conclusion has been validated at our institution as well. It is expected that the utility of FNA will further expand as more molecular tests that require only minimal specimen volumes are developed.

In the setting of FNA cytology, the diagnosis of melanoma is certainly considered much more frequently than it is made, probably because a vast array of morphologic images is potentially attached to melanoma and they can cytologically mimic other neoplastic processes. The constituent morphological categories include spindle cell, nodular, and desmoplastic lesions as well as unusual variants such as small cell, rhabdoid, signet-ring-cell, myxoid, balloon-cell, and metaplastic (melanoma with osteocartilaginous differentiation),[13–18] among others. Because of this diversity, a cytologic diagnosis of melanoma is rarely rendered outright based only on morphologic analysis alone. One needs to integrate clinical information and results of ancillary tests, such as immunocytochemical (ICC) stains, before a final interpretation is made. However, knowledge of clinical and cytomorphologic features of melanoma is necessary to guide the use of supplementary evaluations effectively.

The following discussion is a brief review of common and unusual cytomorphologic features of melanoma, as well as a few possible pitfalls in the diagnosis of that tumor. For the foreseeable future, a problematic issue is needed for cytopathologists to procure sufficient diagnostic material, and, at the same time, obtain needed material for molecular studies at the time that FNA is performed. A high level of diagnostic suspicion and knowledge of the potential morphological features of melanoma are necessary in that process. Melanoma is occasionally called "the great imitator," a well-deserved moniker. Herein we present some, but not all, of the answers to the nearly-rhetorical question—"What does a melanoma look like?"

Clinical history

It cannot be over-emphasized that the practice of cytopathology requires a complete view of the clinical context, and that statement definitely applies to melanoma in particular. At our institution over the past 2 years, only 4 of 21 aspirated cases of melanoma were interpreted as such in the absence of a clinical history of primary melanoma. Chen et al.[8] likewise reported that 22% of their cases of FNA-recognized melanoma also were unassociated with a known primary lesion. The pre-aspiration probability of melanoma as a diagnosis is also affected by the anatomical site that is to be aspirated. A meta-analysis by Hall and coworkers showed that FNAs that were done to evaluate the cause of isolated lymphadenopathy in patients with melanoma often resulted in diagnoses of benign, reactive conditions rather than metastasis. False-negative results were encountered most frequently in axillary lymph node aspirations. Subcutaneous nodules and pulmonary nodules usually yielded an interpretation of metastatic disease, and negative results in that particular context typically indicated that sampling was inadequate.[7]

Historical information and the availability of prior diagnostic material for comparison can prevent mistakes and reduce the application of unnecessary ICC stains in some cases. Nonetheless, up to 20% of melanoma patients develop second non-melanocytic primary neoplasms, and therefore rather liberal use immunostains is still prudent in this setting.[19]

Smearing pattern and background

Direct smears of metastatic melanomas are likely to be cellular with a predominance of single cells (Fig. 1). The basic biological characteristics of melanomas may underlie this tendency, because the expression of adhesion molecules lessens in the transformation of non-neoplastic cells to those seen in malignant melanomas.[20,21] Perry et al.[19] found that

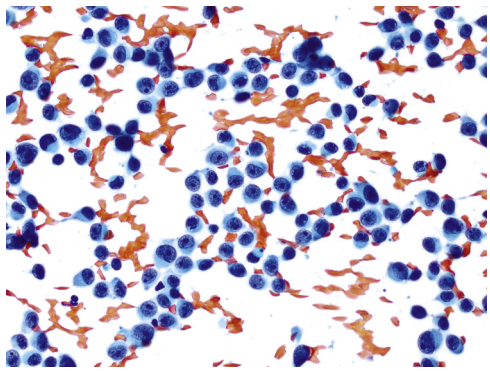

Fig. 1 – These malignant cells show very little cohesion, plasmacytoid nuclear placement, and prominent nucleoli. The lack of cohesion discourages the thought of an epithelial malignancy. (Pap stain 200× magnification.)