Cytologic Features of Metastatic and Recurrent Melanoma in Patients With Primary Cutaneous Desmoplastic Melanoma

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Key Words: Cytology; Desmoplastic melanoma; Fine-needle biopsy; Metastatic melanoma; Skin

Abstract

Desmoplastic melanoma (DM) is a rare subtype of melanoma characterized by malignant spindle cells associated with prominent fibrocollagenous stroma. Primary melanomas may be entirely desmoplastic (“pure” DM) or exhibit a desmoplastic component admixed with a nondesmoplastic component (“combined” DM). The cytologic features of only 5 cases of DM have been reported previously.

Fine-needle biopsy (FNB) specimens from 20 recurrent or metastatic lesions in patients with cutaneous DM and 20 recurrent or metastatic lesions from patients with primary cutaneous non-DM were examined and compared. FNB specimens of patients with DM were less cellular ($P = .009$) and less often exhibited intranuclear cytoplasmic invaginations ($P = .008$) and mitotic figures ($P = .006$) than specimens from patients with non-DM. “Combined” DMs were more commonly composed of epithelioid cells ($P = .017$) and less often contained bizarre/giant tumor cells ($P = .010$) than did “pure” DMs.

Recurrent and metastatic DM has a range of cytologic appearances. Awareness of the cytologic features and careful clinicopathologic correlation will assist in accurate FNB diagnosis.

Melanoma exhibits a wide range of morphologic appearances in histologic specimens. Cytologic material containing melanoma is generally obtained from recurrent and/or metastatic tumors. The material is usually procured by fine-needle biopsy (FNB), which has been shown in several studies to be a procedure with high accuracy for the diagnosis of metastatic melanoma.1-5 The cytologic features of metastatic melanoma have been described in several studies.1-8

Desmoplastic melanoma (DM) is a rare subtype of melanoma, which typically arises in sun-damaged skin of the head and neck region, often in elderly patients. It is characterized by spindle cells separated by fibrocollagenous stroma and exhibits a propensity for neurotropism.9-12 The cytologic features of DM have been infrequently reported in the literature; to our knowledge, only 5 cases have been described, as single cases in large series of metastatic tumors or as isolated case reports.13-17 The aims of this study were to document the cytopathologic features of metastatic and recurrent melanoma in a large series of patients from the Sydney Melanoma Unit (SMU), Sydney, Australia, with histologically confirmed primary cutaneous DM and to compare them with the features of metastatic and recurrent lesions in patients with non-DMs.

Materials and Methods

We identified 20 FNB specimens (FNBs performed between March 1993 and March 2005) of recurrent and/or metastatic melanoma from patients with primary cutaneous...
DM from the databases of the Department of Anatomical Pathology, Royal Prince Alfred Hospital and the SMU. We also retrieved 20 consecutive FNB specimens of recurrent or metastatic lesions in patients with non-desmoplastic primary cutaneous melanoma. The procedures involved in the performance and processing of the FNB specimens have been described elsewhere.\textsuperscript{1}

The histopathologic slides of the primary lesions and the cytologic smears of the recurrent and metastatic tumors were reviewed by a pathologist (R.M.). The following clinical features were evaluated in each case: patient age (at diagnosis of the primary tumor), sex, site of the primary and recurrent or metastatic melanoma, and the interval between the diagnosis of the primary and the metastatic or recurrent tumor. For the DMs, the primary tumors were classified as “pure” or “combined” as per the criteria described by Busam et al.\textsuperscript{18} Briefly, DMs were classified as pure if the overwhelming majority (≥90%) of the invasive tumor was associated with prominent stromal fibrosis and as combined if densely cellular tumor foci without stromal fibrosis (ie, non-DM) constituted more than 10% of the entire tumor. The following cytopathologic features were assessed: cellularity (low, moderate, or high), cell shape (epithelioid, spindle, and/or bizarre), degree of nuclear pleomorphism (mild, moderate, or marked), presence and size of nucleoli, presence of intranuclear cytoplasmic invaginations (pseudoinclusions), presence of melanin pigment and necrotic debris, and the results of immunocytochemical analysis. Features of the cytologic material obtained from patients with primary pure DM, combined DM, and non-DM were compared.

Differences in the cytologic features between the groups (cellularity, cell shape, presence of bizarre cells, degree of nuclear pleomorphism, size of nucleoli, presence of intranuclear cytoplasmic invaginations, and presence of melanin pigment and necrotic debris) were assessed by using the $\chi^2$ test. A $P$ value of less than .05 was considered statistically significant.

\begin{table}
\centering
\caption{Clinical and Pathologic Features in Patients With Primary Cutaneous DM}
\begin{tabular}{llllllll}
\hline
Patient No./Sex/Age (y)\textsuperscript{*}/Case No. & Site of Primary Tumor & Breslow Thickness (mm) & Clark Level & Ulceration & Mitotic Rate (per mm\textsuperscript{2}) & Neurotropism & Type of DM & Site of Recurrent/Metastatic Tumor & Time (mo)\textsuperscript{†} \\
\hline
1/M/55.6 & Back & 1.6 & 4 & + & 4 & – & Combined & Supravclavicular & 42 \\
2/M/73.8 & Ear & 1.2 & 4 & – & 2 & – & Combined & Neck & 34 \\
3/F/48.3 & Toe & 4.0 & 4 & – & 2 & – & Combined & Groin & 22 \\
5/M/52.7 & Foot (heel) & 9.9 & 5 & + & 8 & – & Combined & Knee (popliteal) & 9 \\
6/M/49.7 & Back & 4.0 & 4 & + & 8 & – & Combined & Back/axilla & 15 \\
7/M/50.0 & Back & 7.5 & 4 & + & 12 & – & Combined & Axilla & 12 \\
8/M/91.4 & Forearm & 1.8 & 4 & + & 4 & – & Combined & Axilla & 42 \\
9/M/41.2 & Temple & 4.5 & 5 & + & 20 & – & Combined & Temple/parotid & 5 \\
10/Back & 3.8 & 4 & – & 1 & + & Combined & Chest & 48 \\
11/Back & 3.8 & 4 & – & 1 & + & Combined & Lung & 49 \\
12/M/89.5 & Arm & 4.6 & 4 & + & 15 & + & Combined & Neck & 14 \\
13/M/78.4 & Scalp & 6.5 & 5 & + & <1 & + & Pure & Neck & 15 \\
14/M/59.9 & Chest & 2.9 & 4 & – & 3 & + & Pure & Lung & 73 \\
15/M/81.0 & Hand & 3.2 & 4 & – & 2 & + & Pure & Axilla & 11 \\
16/M/75.7 & Hand & 3.2 & 4 & – & 2 & + & Pure & Axilla & 19 \\
17/M/49.4 & Forehead & 5.1 & 4 & – & 14 & – & Pure & Preauricular & 4 \\
18/F/62.0 & Finger & 2.2 & 4 & + & 7 & – & Combined & Axilla & 5 \\
19/Back & 4.0 & 5 & – & 3 & + & Combined & Pleural fluid & 40 \\
20/Back & 4.0 & 5 & – & 3 & + & Combined & Pleural fluid & 41 \\
\hline
\end{tabular}
\end{table}

DM, desmoplastic melanoma; –, absent; +, present.

\textsuperscript{*}At diagnosis of primary tumor.

\textsuperscript{†}Between diagnosis of primary tumor and recurrence/metastasis.
### Results

During the period March 1993 to March 2005, 14,131 patients with melanoma were referred to the SMU, of which 758 (5.4%) were desmoplastic melanomas. There were 20 FNB specimens from 16 patients (14 men and 2 women) with primary cutaneous DM. The clinical and histologic features of the DMs are summarized in Table 1. Of the cases, 18 were FNB specimens and 2 cases were pleural fluid specimens.

The smears showed a range of appearances Table 2. The degree of cellularity varied from low (10 cases [50%]) to moderate (4 cases [20%]) to high (6 cases [30%]). The smears were composed of purely epithelioid cells in 9 cases (45%) Image 1 and Image 2, a mixture of spindle and epithelioid cells in 9 cases (45%) Image 3, and purely spindle cells in 2 cases (10%) Image 4. Three cases (15%) contained bizarre/giant tumor cells Image 5.

Of the cases, 19 (95%) exhibited moderate or marked nuclear pleomorphism, and nucleoli were prominent in 11 cases (55%; Images 2B and 4B). Occasional naked nuclei were seen in many cases. Melanin pigment was present in tumor cells.

### Table 2

Cytopathologic Features of Recurrent/Metastatic Lesions in Patients With Primary Cutaneous Desmoplastic Melanoma

<table>
<thead>
<tr>
<th>Specimen/Case No.</th>
<th>Cell Type</th>
<th>Cellularity</th>
<th>Nuclear Pleomorphism</th>
<th>Nucleoli</th>
<th>Mitoses</th>
<th>INCIs</th>
<th>Necrosis</th>
<th>Pigment</th>
<th>Positive IC</th>
<th>Cell Type in Histologic Specimen (When Available)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FNB</td>
<td>Epithelioid with focal spindle component</td>
<td>2+</td>
<td>2+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>ND</td>
<td>Predominantly spindle</td>
</tr>
<tr>
<td>1</td>
<td>Spindle</td>
<td>+</td>
<td>2+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>ND</td>
<td>Epithelioid</td>
</tr>
<tr>
<td>2</td>
<td>Epithelioid</td>
<td>3+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>S-100; HMB-45</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Spindle &gt; epithelioid</td>
<td>3+</td>
<td>2+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>S-100; HMB-45</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Spindle</td>
<td>+</td>
<td>3+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>ND</td>
<td>Epithelioid and spindle</td>
</tr>
<tr>
<td>5</td>
<td>Epithelioid</td>
<td>2+</td>
<td>2+</td>
<td>2+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>S-100; HMB-45</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Epithelioid</td>
<td>3+</td>
<td>2+</td>
<td>2+</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>S-100; HMB-45</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Epithelioid</td>
<td>3+</td>
<td>2+</td>
<td>2+</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>S-100; HMB-45</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Spindle with epithelioid</td>
<td>2+</td>
<td>2+</td>
<td>2+</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>S-100; HMB-45</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Epithelioid with small spindle component and occasional bizarre giant cells</td>
<td>3+</td>
<td>3+</td>
<td>2+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>ND</td>
<td>Predominantly spindle epidermoid</td>
</tr>
<tr>
<td>10</td>
<td>Epithelioid</td>
<td>+</td>
<td>3+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>ND</td>
<td>Epithelioid</td>
</tr>
<tr>
<td>11</td>
<td>Epithelioid</td>
<td>+</td>
<td>2+</td>
<td>3+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>ND</td>
<td>Predominantly spindle epidermoid</td>
</tr>
<tr>
<td>12</td>
<td>Epithelioid</td>
<td>+</td>
<td>3+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>ND</td>
<td>Predominantly spindle epidermoid</td>
</tr>
<tr>
<td>13</td>
<td>Epithelioid</td>
<td>+</td>
<td>3+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>ND</td>
<td>Predominantly spindle epidermoid</td>
</tr>
<tr>
<td>14</td>
<td>Epithelioid with spindle</td>
<td>+</td>
<td>2+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>ND</td>
<td>Predominantly spindle epidermoid</td>
</tr>
<tr>
<td>15</td>
<td>Epithelioid</td>
<td>+</td>
<td>3+</td>
<td>3+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>S-100; HMB-45</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Mainly spindle with occasional epithelioid and bizarre giant cells</td>
<td>2+</td>
<td>3+</td>
<td>3+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>ND</td>
<td>Predominantly spindle epidermoid</td>
</tr>
<tr>
<td>17</td>
<td>Mainly spindle with occasional epithelioid and bizarre giant cells</td>
<td>+</td>
<td>3+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>ND</td>
<td>Predominantly spindle epidermoid</td>
</tr>
<tr>
<td>18</td>
<td>Epithelioid</td>
<td>3+</td>
<td>2+</td>
<td>2+</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>S-100; HMB-45</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Epithelioid</td>
<td>+</td>
<td>2+</td>
<td>2+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>S-100; HMB-45</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Epithelioid</td>
<td>+</td>
<td>2+</td>
<td>2+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>S-100; HMB-45</td>
<td></td>
</tr>
</tbody>
</table>

FNB, fine-needle biopsy; IC, immunochemical studies; INCIs, intranuclear cytoplasmic invaginations (pseudoinclusions); ND, not done.

* Scoring was as follows: for cellularity: +, low; 2+, moderate; 3+, high; nuclear pleomorphism: +, mild; 2+, moderate; 3+, marked; nucleoli: –, inconspicuous; +, small; 2+, intermediate; 3+, prominent; and mitoses, INCIs, necrosis, and pigment: –, absent; +, present.
or in macrophages in 6 cases (30%; Image 2A), and necrotic material was seen in the background in 4 cases (20%). There was sufficient material for immunochemical stains in 9 cases (45%). The tumor cells were positive for S-100 alone (6 cases, 5 of which were combined DM and 1 of which was pure DM) or S-100 and HMB-45 (3 cases, all combined DM; Table 2).

The smears in 5 cases (25%) from 4 patients with primary pure DM were composed of a mixture of spindle and epithelioid cells, with spindle cells predominating in 3 of the cases. The smears in 15 cases (75%) from 12 patients with primary combined DM were composed of epithelioid cells (9 cases [60%]), a mixture of spindle and epithelioid cells (4 cases [27%]), or spindle cells (2 cases [13%]).

The cytologic features of the tumors in patients with primary cutaneous non-DM are summarized in Table 3. The smears showed predominantly high cellularity (15 cases [75%]). The smears were composed of purely epithelioid cells in 15 cases (75%) or a mixture of epithelioid and spindle cells (the former predominating) in 5 cases (25%). Five cases (25%) contained bizarre/giant tumor cells. All cases exhibited moderate or marked nuclear pleomorphism, and nucleoli were intermediate-sized or prominent in 11 cases (55%). Melanin pigment was present in tumor cells or in macrophages in 4 cases (20%), and necrotic material was seen in the background in 3 cases (15%). There was sufficient material for immunochemical stains in 13 cases (65%).

The FNB specimens of patients with DM tended to be of lower cellularity ($P = .009$) and less often exhibited intranuclear cytoplasmic invaginations ($P = .008$) and mitotic figures ($P = .006$) than non-DM specimens. There were no statistically significant differences between the DM and non-DM groups in the cellular shape, degree of nuclear pleomorphism, or the presence of bizarre/giant tumor cells, nucleoli, melanin pigment, and necrosis in the cytology specimens.
When the non-DM cases were compared with the pure DM and combined DM groups, distinct patterns of statistically significant differences emerged. Pure DMs showed lower cellularity ($P = .003$) and less often exhibited intranuclear cytoplasmic invaginations ($P = .027$) and mitotic figures ($P = .041$) than non-DMs. FNB specimens from non-DMs were more often composed of epithelioid cells than those from pure DMs ($P = .002$). Combined DMs, on the other hand, showed lesser degrees of nuclear pleomorphism ($P = .011$) and less prominent nucleoli ($P = .046$) and more often exhibited intranuclear cytoplasmic invaginations ($P = .036$) than did non-DMs.

Comparison of the FNB specimens from the pure DM and combined DM groups showed that the latter were more commonly composed of epithelioid cells ($P = .017$) and less often contained bizarre/giant tumor cells ($P = .010$). There were no statistically significant differences between the pure and combined groups in the degree of cellularity and nuclear pleomorphism or in the presence of mitotic figures, intranuclear cytoplasmic invaginations, nucleoli, melanin pigment, or necrosis.
Discussion

Melanoma can spread via lymphatic routes, by direct extravascular migration, and hematogenously, and, therefore, metastases may occur in a variety of body sites, including regional lymph nodes, skin and subcutis, deep soft tissues, and visceral organs such as lung, liver, and brain. In histologic sections, melanoma is well known to exhibit a diverse range of morphologic appearances, and several architectural and cytologic variants of primary melanoma have been described. Histologically, metastatic melanoma usually exhibits a nested, fascicular, or sheet-like growth pattern. It often displays nuclear pleomorphism, mitotic activity, and necrosis. It is composed predominantly of epithelioid cells, but varying combinations of epithelioid cells, spindle cells, and bizarre and/or giant tumor cells may occasionally be seen. Melanin pigment may be prominent, subtle, or absent.

Smears prepared from FNB samples of metastatic melanoma can show a wide range of appearances. As shown in this study, cytologic preparations of specimens obtained from metastatic non-DM usually show high cellularity. The cells are often dispersed singly, although tumor cell groups are not uncommonly found. The cells are usually epithelioid in shape, but in some cases tumors are composed of predominantly spindle cells or an admixture of epithelioid and spindle cells. They usually contain moderate amounts of cytoplasm, and cytoplasmic melanin pigment is identified in tumor cells in 28% to 60% of cases. Melanin pigment may also be seen in macrophages and in the background. The cells exhibit moderate to marked nuclear pleomorphism and, in some cases, contain binucleate and multinucleate cells. Nuclear chromatin is finely or coarsely granular, and nuclear membrane irregularities may be seen. Nucleoli are often prominent, and some cells may contain large eosinophilic macronucleoli.

In Image 4, Metastatic tumor in a patient with primary “pure” desmoplastic melanoma (DM). A, Smear of tumor composed predominantly of spindle cells arranged in crowded and loosely cohesive groups (Papanicolaou, ×100). B, Spindle cells exhibiting cytologic atypia and prominent nucleoli (Papanicolaou, ×400). C, Histologic section of primary pure DM showing atypical spindle cells amid collagenous stroma; a mitotic figure (arrow) is present (H&E, ×200).
cytoplasmic invaginations (pseudoinclusions) may be seen. The background often contains blood and necrotic debris (the latter in 4%-14% of cases). Immunochemistry may be performed on smears or on cell-block preparations, and the tumor cells are often positive for S-100, HMB-45, and Melan-A.

Primary cutaneous DM is characterized histologically by spindle cells exhibiting variable (usually mild to moderate) cytologic atypia, separated by collagen fibers or fibrous stroma. The degree of cellularity and stromal fibrosis is variable. The tumor cells usually lack cytoplasmic pigment. Immunohistochemically, the tumor cells are positive for S-100 but are usually negative for other melanocytic markers such as HMB-45 and Melan-A. Metastases from primary cutaneous DM may be composed of spindle cells and/or epithelioid cells.

In addition to tumors entirely or almost entirely composed of desmoplastic areas, melanomas of any histologic subtype may contain desmoplastic areas. Some authors have categorized DM as pure DM if desmoplasia is prominent throughout the entire invasive tumor and as "mixed" DM or combined DM if only part of an otherwise non-DM exhibits desmoplasia.

The cytologic features of DM have very rarely been reported, usually as isolated case reports. The reports describe variably sized groups of spindle cells, sometimes with a fascicular arrangement, with focal areas of cellular dissociation. The cells exhibit mild to moderate cytologic atypia, and the cell nuclei are hyperchromatic with small but conspicuous nucleoli. Some reported cases showed little cytologic atypia in the majority of spindle cells (which resemble fibroblasts), with only rare spindle cells exhibiting significant atypia. Naked nuclei were prominent in 1 case. Pigment

### Table 3: Cytopathologic Features of Recurrent/Metastatic Tumors in Fine-Needle Biopsy Specimens From Patients With Nondesmoplastic Primary Cutaneous Melanoma

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Cell Type</th>
<th>Cellularity</th>
<th>Nuclear Pleomorphism</th>
<th>Nucleoli</th>
<th>Mitoses</th>
<th>INCIs</th>
<th>Necrosis</th>
<th>Pigment</th>
<th>Positive IC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Epithelioid</td>
<td>3+</td>
<td>2+</td>
<td>2+</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>S-100; HMB-45</td>
</tr>
<tr>
<td>2</td>
<td>Epithelioid plus focal spindle component</td>
<td>+ 2+</td>
<td>+ 2+</td>
<td>+ 2+</td>
<td>– 2+</td>
<td>– 2+</td>
<td>– 2+</td>
<td>– 2+</td>
<td>S-100; HMB-45</td>
</tr>
<tr>
<td>3</td>
<td>Epithelioid</td>
<td>3+</td>
<td>3+</td>
<td>3+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>S-100; HMB-45</td>
</tr>
<tr>
<td>4</td>
<td>Epithelioid plus occasional bizarre giant cells</td>
<td>3+</td>
<td>3+</td>
<td>3+</td>
<td>+</td>
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<td>+</td>
<td>–</td>
<td>S-100; HMB-45</td>
</tr>
<tr>
<td>5</td>
<td>Epithelioid</td>
<td>3+</td>
<td>3+</td>
<td>3+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>S-100; HMB-45</td>
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<tr>
<td>6</td>
<td>Epithelioid plus occasional bizarre giant cells</td>
<td>3+</td>
<td>3+</td>
<td>3+</td>
<td>+</td>
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<td>+</td>
<td>–</td>
<td>S-100; HMB-45</td>
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<tr>
<td>7</td>
<td>Epithelioid</td>
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<td>3+</td>
<td>3+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>S-100; HMB-45</td>
</tr>
<tr>
<td>8</td>
<td>Epithelioid plus occasional bizarre giant cells</td>
<td>3+</td>
<td>3+</td>
<td>3+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>S-100; HMB-45</td>
</tr>
<tr>
<td>9</td>
<td>Epithelioid</td>
<td>3+</td>
<td>3+</td>
<td>3+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>S-100; HMB-45</td>
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<tr>
<td>10</td>
<td>Epithelioid</td>
<td>3+</td>
<td>3+</td>
<td>3+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>S-100; HMB-45</td>
</tr>
<tr>
<td>11</td>
<td>Epithelioid plus occasional bizarre giant cells</td>
<td>3+</td>
<td>3+</td>
<td>3+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>S-100; HMB-45</td>
</tr>
<tr>
<td>12</td>
<td>Epithelioid</td>
<td>3+</td>
<td>3+</td>
<td>3+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>S-100; HMB-45</td>
</tr>
<tr>
<td>13</td>
<td>Epithelioid</td>
<td>3+</td>
<td>3+</td>
<td>3+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>S-100; HMB-45</td>
</tr>
<tr>
<td>14</td>
<td>Epithelioid plus spindle</td>
<td>3+</td>
<td>3+</td>
<td>3+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>S-100; HMB-45</td>
</tr>
<tr>
<td>15</td>
<td>Epithelioid plus focal spindle component</td>
<td>3+</td>
<td>3+</td>
<td>3+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>S-100; HMB-45</td>
</tr>
<tr>
<td>16</td>
<td>Epithelioid plus occasional bizarre giant cells</td>
<td>3+</td>
<td>3+</td>
<td>3+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>S-100; HMB-45</td>
</tr>
<tr>
<td>17</td>
<td>Epithelioid plus spindle</td>
<td>3+</td>
<td>3+</td>
<td>3+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>S-100; HMB-45</td>
</tr>
<tr>
<td>18</td>
<td>Epithelioid</td>
<td>3+</td>
<td>3+</td>
<td>3+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>S-100; HMB-45</td>
</tr>
<tr>
<td>19</td>
<td>Epithelioid plus focal spindle component</td>
<td>3+</td>
<td>3+</td>
<td>3+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>S-100; HMB-45</td>
</tr>
<tr>
<td>20</td>
<td>Epithelioid</td>
<td>3+</td>
<td>3+</td>
<td>3+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>S-100; HMB-45</td>
</tr>
</tbody>
</table>

IC, immunohistochemical studies; INCIs, intranuclear cytoplasmic invaginations (pseudoinclusions).

Scoring was as follows: for cellularity: +, low; 2+, moderate; 3+, high; nuclear pleomorphism: +, mild; 2+, moderate; 3+, marked; nucleoli: –, inconspicuous; +, small; 2+, intermediate; 3+, prominent; and mitoses, INCIs, necrosis, and pigment: –, absent; +, present.
or intranuclear cytoplasmic invaginations were not identified. The tumor cells were weakly positive for S-100 but negative for HMB-45.\textsuperscript{13-17}

In our series, the degree of cellularity of the smears was significantly lower in the cases with primary DM compared with those with primary non-DM ($P = .003$). In our experience with melanomas in general, paucity of cellular material can be a significant cause of an unsatisfactory procedure. That the smears in the cases with primary combined DM were composed of epithelioid cells, a mixture of spindle and epithelioid cells, or spindle cells is not surprising because the primary tumors were composed of desmoplastic and nondesmoplastic components. Histologically, the metastatic and recurrent lesions in all 5 cases of primary pure DM were composed predominantly of spindle cells (Table 2). It is interesting that the FNB specimens from all 5 cases contained spindle \textit{and} epithelioid cells. Because the definition of pure DM requires that more than 90\% (but not 100\%) of the tumor be desmoplastic, epithelioid cells in some cases of recurrent or metastatic pure DM may derive from the nondesmoplastic component of the tumor. An alternative explanation is that melanoma cells may undergo phenotypic variations in recurrences or with disease progression, the latter hypothesis supported by our personal observations and the results of some cell culture studies of melanoma.\textsuperscript{31} In contrast, the smears from cases with primary non-DM were composed exclusively or predominantly of epithelioid cells.

Because cytologic preparations of recurrent and metastatic DM often include a significant spindle cell component, the cytologic differential diagnosis of DM includes benign and malignant spindle cell lesions. The importance of clinico-pathologic correlation in achieving the correct diagnosis cannot be overemphasized. Features such as a history of a previous cutaneous DM or other tumor or imaging findings suggestive of an organizing hematoma, to name but 2 examples, may be of considerable help in accurate diagnosis.

In locally recurrent lesions (such as at the site of previous excision of a DM), reactive conditions such as exuberant mesenchymal repair (scar) or fibroblastic proliferation surrounding organizing hematoma should be considered in the differential diagnosis.\textsuperscript{1,13} Although some cases of DM may exhibit significant cytologic atypia (often in only a proportion of cells), others exhibit lesser levels of atypia, and, in such cases, there exists some overlap in the degree of cytologic atypia and in the aforementioned reactive conditions. Therefore, caution is warranted in making a definitive diagnosis of malignancy, particularly when interpreting poorly cellular smears, smears exhibiting mild cytologic atypia, and smears obtained from lesions located at sites of previous surgery. The presence of melanin pigment, although not seen in all cases, favors DM. However, hemosiderin may be present in the background and in macrophages in smears from organizing hematoma and may mimic melanin. Stains such as Perls and Fontana-Masson aid in their distinction. Immunohistochemically, DM usually exhibits positivity for S-100, which may be in only a proportion of cells, while other melanoma markers such as HMB-45 are usually negative. It is important to note that S-100+ spindle cells (likely fibroblasts) may be seen in scars.\textsuperscript{32}

The cytologic features of benign or low-grade spindle cell lesions such as benign nerve sheath tumors (schwannoma and neurofibroma), dermatofibroma, and fibromatosis may resemble DM. Spindle cell or pleomorphic sarcomas and spindle cell carcinomas also enter the differential diagnosis and may be impossible to distinguish from DM on the basis of their cytomorphic features alone.\textsuperscript{13} In such cases, the diagnosis can usually be confirmed by correlation with the clinical and radiologic features, and, if sufficient material can be obtained, the results of ancillary immunohistochemical studies. Obtaining sufficient cytologic material for immunohistochemical studies may be difficult, particularly in tumors of low cellularity with prominent fibrosis (such as a deposit exhibiting “desmoplastic” morphologic features, composed of a small number of spindle cells enmeshed within abundant fibrocolagenous stroma) or if there is necrosis within the lesion. In the present study, sufficient material for immunohistochemical studies was obtained in only 9 of 20 cases. An alternative in such a situation is to perform immunohistochemical studies on an unstained or a destained smear.

Malignant peripheral nerve sheath tumor may be particularly difficult to distinguish from DM in cytologic preparations. In addition to similar morphologic features, both may be positive for S-100, although malignant peripheral nerve sheath tumors, in contrast with benign nerve sheath tumors, are often S-100− or only focally S-100+. HMB-45 is negative in both tumors.\textsuperscript{11,12} In difficult cases, ultrastructural examination may be helpful.

Recurrent or metastatic tumors in patients with DM exhibit a range of cytologic features, recognition of which, along with clinico-pathologic correlation, is important in establishing the correct diagnosis and in distinguishing metastatic DM from other entities.

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References