Undifferentiated Tumor

True Identity by Immunohistochemistry

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● Context.—“Undifferentiated tumor” refers to a heterogeneous group of neoplasms with little or no evidence of differentiation on routine light microscopic morphology.

Objective.—To identify the true identity of undifferentiated tumors by immunohistochemical analysis.

Data Sources.—Review of the pertinent literature and the authors’ experience.

Conclusions.—For treatment and prognostic evaluation, it is crucial to delineate whether an undifferentiated neoplasm is epithelial, mesenchymal, melanocytic, or hematopoietic in nature. Application of a screening panel to demonstrate the expression of markers of major lineages is fundamental for determination of the broad category of neoplasia. Because poorly differentiated carcinomas and in particular sarcomatoid carcinomas are known to be heterogeneous in their antigen expression, several epithelial markers in combination may be required to establish the carcinomatous nature of tumor. A diagnostic misinterpretation as a consequence of occasional aberrant or unexpected antigen expression is best avoided by using a broad panel that includes both antibodies that are anticipated to be positive and those that are expected to be negative. In this treatise, the immunohistochemical dissection of undifferentiated tumors on the basis of their morphologic features is outlined, supplemented with algorithmic immunohistochemical analysis for each morphologic category of small round cell tumors, carcinomatous tumors, sarcomatous (or sarcoma-like) tumors, and tumors with histologically overlapping features, including hematolymphoid malignancies, melanoma, and sarcomas with epithelioid appearance. The utility of several organ- or tissue-specific markers in the context of undifferentiated tumors is reviewed.

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The term undifferentiated tumor has been used in reference to a heterogeneous group of tumors with little or no evidence of differentiation. Some may link this terminology to morphologically undifferentiated neoplasms that cannot be otherwise classified, even with the application of immunohistochemistry. In our view, however, such tumors are extremely rare and in most instances further sampling or application of ancillary tests should help to recognize them as a specific tumor type. For such reason, in this review we apply the term undifferentiated to tumors lacking evidence of lineage differentiation on the basis of routine light microscopic morphology alone.

An undifferentiated malignant tumor represents either a metastasis of unknown origin or a primary neoplasm without obvious cell line of differentiation. It should be noted that undifferentiated tumor generally implies a high-grade malignancy, frequently associated with pleomorphic to anaplastic appearance. Therefore, low-grade neoplasms but without an obvious lineage of differentiation (eg, monomorphic spindled cell tumors) or low-grade tumors not infrequently encountered in the context of metastasis of unknown origin are not included in this discussion.

For treatment purposes, it is crucial to determine whether an undifferentiated neoplasm is epithelial, mesenchymal, or hematopoietic. In general, the diagnosis of lymphoma for an undifferentiated tumor predicts a better clinical outcome compared with that of carcinoma. The value of immunohistochemical procedures for identification of the true identity of undifferentiated tumors has been proved by studies in which approximately 90% of tumors posing diagnostic difficulties by morphology could be accurately classified by exploiting immunohistochemistry.

Even in undifferentiated tumors, subtle features of epithelial versus mesenchymal differentiation can often be appreciated, which assist the immunohistochemical approach to these tumors. Hints for epithelial differentiation include epithelioid cells (round to oval cells) with nesting arrangement and a desmoplastic stroma with feeding vessels separating tumor cell nests (Figure 1). In contrast, mesenchymal differentiation is suggested by a diffuse arrangement of spindled cells (Figure 2), without reactive stroma, but with feeding vessels in between tumor cells. Some tumors, however, may not fit into either of these 2 categories because of their overlapping histologic features (Figure 3), for example, sarcomatoid carcinoma, melanoma, lymphoma, neuroendocrine tumors, and sarcoma with epithelioid cells.

Immunohistochemical dissection of undifferentiated tumors is also helped by categorizing them into small round...
blue cell tumors (SRCTs) or large cell tumors. The latter group is further divided into (1) carcinomatous tumors, (2) sarcomatous or sarcoma-like tumors, and (3) tumors with overlapping features. Each category entails a broad list of entities from epithelial, mesenchymal, hematopoietic, or melanocytic lineage in the differential diagnosis.

In the following section, the immunohistochemical procedure for a broad lineage determination of undifferentiated tumors is discussed, followed by immunohistochemical analysis of each individual category of SRCTs, carcinomatous tumors, sarcomatous (or sarcoma-like) tumors, and tumors with overlapping features, supplemented with diagnostic algorithms. It is emphasized that the outlined algorithmic immunohistochemical approach is neither meant to be comprehensive nor intended to be an absolute method for immunohistochemical dissection of these tumors. In reality, each tumor requires an “individually constructed panel” composed of carefully selected antibodies that recognize all reasonable diagnostic possibilities in the context of the tumor's morphology, anatomic site, and clinical/radiologic findings.

**BROAD LINEAGE DETERMINATION**

The immunohistochemical evaluation of undifferentiated tumors should first aim at determination of the broad category of neoplasia, that is, carcinoma, sarcoma, lymphoma, or melanoma. A screening panel to demonstrate the expression of markers of major lineages (ie, epithelial, mesenchymal, lymphoid, and melanocytic) often provides the first clue to the nature of an undifferentiated tumor. In certain circumstances, adjuvant immunostains are added; thus, placental alkaline phosphatase (PLAP) and OCT3/4, markers for germ cell tumors (GCTs), may be included for tumors in younger men in view of the high incidence of GCTs in this age group. Based on the result of the screening panel, a more detailed or specific panel is commonly followed to further subclassify the tumor or confirm a particular diagnosis.

**Screening Markers for Epithelial Lineage**

**Cytokeratins.**—The low-molecular-weight cytokeratins (LMW CKs), including CK8, CK18, and CK19, recognized by the antibodies CAM 5.2 or 35BH11, and a cocktail of keratins (pankeratin), recognized by the antibody AE1/AE3, are useful screening markers for the recognition of epithelial differentiation. Because poorly differentiated carcinomas are known to be heterogeneous in their expression of antigens recognized by epithelial markers, when a negative result is obtained with a single antibody and the diagnosis of carcinoma is still suspected, it is prudent to use additional antibodies in a backup panel. In a study of 98 poorly differentiated carcinomas, CAM 5.2 and epithelial membrane antigen (EMA) each detected epithelial differentiation of 71% of the cases, whereas a combined CAM 5.2 and EMA elucidated the epithelial nature of 99%.

Sarcomatoid carcinomas are in particular known to be unpredictable in regard to their CK expression; therefore,
it is sometimes required to use several markers in combination to detect the epithelial differentiation of these tumors (see “Sarcomatoid Carcinoma”). In addition, CK may not be detectable in certain carcinomas; for example, it is known that CK expression in adrenocortical carcinomas is often diminished to levels too low to be recognized following the deleterious effects of fixation.5–7

Cytokeratin expression, most frequently with LMW CKs, has been occasionally described in a variety of sarcomas8–9 and rarely in hematopoietic malignancies10–14 and melanocytic lesions.9,15,16 Aberrant CK staining in nonepithelial malignancies, however, has a weak, focal, and patchy staining, which contrasts with the generally diffuse and strong staining seen in carcinomas or sarcomatoid carcinomas. Conversely, a true strong CK expression, which is frequently associated with a morphologic appearance of epithelial differentiation, is also seen in certain sarcomas9 (see “Sarcomas With Epithelioid Appearance”). Hence, caution should be taken to avoid overinterpretation of CK expression as a specific feature of epithelial tumors.

Epithelial Membrane Antigen.—As mentioned previously, EMA may be used as a supplement to CKs for detection of epithelial differentiation, especially in sarcomatoid carcinoma or those undifferentiated carcinomas that are negative or only focally positive for CKs. A number of epithelial tumors, including GCTs and some endocrine neoplasms such as medullary carcinoma of thyroid and adrenocortical carcinomas, lack immunoreactivity for EMA.26

Epithelial membrane antigen is not entirely specific for carcinomas. Epithelial membrane antigen expression has been seen in some normal and neoplastic hematopoietic cells, including reactive and neoplastic plasma cells,12 lymphoepithelial and histiocytic (L&H) cells in nodular lymphocyte predominant Hodgkin lymphoma,18,19 and neoplastic cells in some T-cell lymphomas17,20; thus, most anaplastic lymphoma kinase (ALK)-positive anaplastic large cell lymphomas (~75%) are EMA positive.21–23

Screening Marker for Mesenchymal Lineage

Vimentin.—Vimentin is the sole intermediate filament characteristic of mesenchymal cells and present in virtually all sarcomas and melanomas and variably in lymphomas.22 The antigenicity of vimentin is best preserved in frozen and alcohol-fixed tissues.22,23 Vimentin, however, suffers poor specificity for mesenchymal neoplasms because it may be coexpressed with CK in a wide range of carcinomas (Table 1).22–24 Therefore, vimentin by itself cannot be used to differentiate mesenchymal from nonmesenchymal neoplasms.

Vimentin/CK Coexpression

Frequent coexpression of vimentin with CK is seen in some carcinomas, for example, renal cell, endometrial, papillary and anaplastic thyroid, and ovarian serous (variably) carcinomas.22,23 Consistent absence of vimentin, on the other hand, is observed in colonic, small intestinal, and prostatic adenocarcinomas or in transitional cell carcinomas.22 The finding of vimentin/CK coexpression helps focus on certain types of epithelial tumors as possible primary sites in the evaluation of metastatic tumors. On the other hand, a number of sarcomas, in particular those with epithelioid appearance, also express CK in addition to vimentin. A selected list of malignant neoplasms frequently demonstrating vimentin/CK coexpression is provided in Table 1.

Screening Markers for Malignant Melanoma

S100 Protein.—S100 protein is regarded as a screening marker for melanoma with more than 95% sensitivity in primary and metastatic sites. A valid positive S100 requires both nuclear and cytoplasmic staining. S100 protein, however, is also expressed in various other lesions, including peripheral nerve sheath, granular cell, cartilaginous and salivary gland tumors, chordomas, Langerhans cell histiocytosis, and occasional adenocarcinomas to varying degrees.25 Thus, to confirm the melanocytic nature of an S100-positive neoplasm, the tumor should be also positive for one or more melanocyte-specific protein (eg, HMB-45 or MART-1/Melan-A).

HMB-45.—HMB-45 is a quite specific marker for melanoma, labeling 90% to 100% of conventional primary melanomas. The positivity rate declines to 80% in recurrent or metastatic melanomas and spindle cell melanomas.26 Desmoplastic melanomas are essentially negative for HMB-45 or other specific melanoma markers.27 HMB-45 positivity is typically not observed in carcinomas, lymphomas, or sarcomas.

Screening Marker for Hematopoietic Malignancies

CD45.—Although CD45 (leukocyte common antigen [LCA]) is known to have high sensitivity (97%) and specificity (nearly 100%) for lymphoid tumors, exceptions have been documented. For example, CD45 is undetectable in most lymphoblastic lymphomas29–32 and is variably expressed in plasma cell neoplasms29,33–35 and anaplastic large T-cell lymphomas.36,37 CD45 immunoreactivity has been considered exquisitely specific for hematopoietic cells29,29; yet, there are exceptional reports of CD45 expression in undifferentiated or neuroendocrine carcinomas.38

Aberrant or Unpredicted Antigen Expression

As stated in several previous examples, an aberrant or unexpected antigen expression should be considered as a source of diagnostic pitfall in the surgical pathology evaluation of undifferentiated tumors. A diagnostic misinterpretation is best avoided by using a broad panel that includes both antibodies that are anticipated to be positive and those that are expected to be negative. The occasional aberrant immunophenotyping must not undermine the

Table 1. Malignant Neoplasms With Coexpression of Vimentin and Cytokeratin

<table>
<thead>
<tr>
<th>Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal cell carcinoma</td>
</tr>
<tr>
<td>Endometrial adenocarcinoma</td>
</tr>
<tr>
<td>Serous ovarian carcinoma</td>
</tr>
<tr>
<td>Thyroid carcinoma, papillary and anaplastic</td>
</tr>
<tr>
<td>Mesothelioma (biphasic)</td>
</tr>
<tr>
<td>Sarcomatoid carcinoma (spindle cell carcinoma)</td>
</tr>
<tr>
<td>Sarcoma</td>
</tr>
<tr>
<td>Synovial sarcoma</td>
</tr>
<tr>
<td>Desmoplastic small round cell tumor</td>
</tr>
<tr>
<td>Malignant rhabdoid tumor</td>
</tr>
<tr>
<td>Epithelioid sarcoma</td>
</tr>
<tr>
<td>Epithelioid angiosarcoma</td>
</tr>
<tr>
<td>Carcinosarcoma</td>
</tr>
</tbody>
</table>

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### Table 2. The Immunoprofile of Small Round Cell Tumors

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>CK</th>
<th>CD45</th>
<th>S100</th>
<th>CD99</th>
<th>Desmin</th>
<th>Myogenin/Myo-D1</th>
<th>CD56</th>
<th>WT1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ewing sarcoma/primitive neuroectodermal tumor</td>
<td>$\approx$</td>
<td>$-$</td>
<td>$-$</td>
<td>$+$</td>
<td>$-$</td>
<td>$-$</td>
<td>$+$</td>
<td>$-$</td>
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<tr>
<td>Rhabdomyosarcoma</td>
<td>$-$</td>
<td>$-$</td>
<td>$-$</td>
<td>$-$</td>
<td>$-$</td>
<td>$+$</td>
<td>$+$</td>
<td>$-$</td>
</tr>
<tr>
<td>Desmoplastic small round cell tumor</td>
<td>$+$</td>
<td>$-$</td>
<td>$-$</td>
<td>$-$</td>
<td>$-$</td>
<td>$+$</td>
<td>$+$</td>
<td>$-$</td>
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<tr>
<td>Poorly differentiated synovial sarcoma</td>
<td>$+$</td>
<td>$-$</td>
<td>$-$</td>
<td>$-$</td>
<td>$-$</td>
<td>$+$</td>
<td>$+$</td>
<td>$-$</td>
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<tr>
<td>Mesenchymal chondrosarcoma</td>
<td>$-$</td>
<td>$-$</td>
<td>$-$</td>
<td>$-$</td>
<td>$-$</td>
<td>$+$</td>
<td>$+$</td>
<td>$-$</td>
</tr>
<tr>
<td>Wilms tumor</td>
<td>$\approx$</td>
<td>$-$</td>
<td>$-$</td>
<td>$-$</td>
<td>$-$</td>
<td>$+$</td>
<td>$+$</td>
<td>$-$</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>$-$</td>
<td>$-$</td>
<td>$-$</td>
<td>$-$</td>
<td>$-$</td>
<td>$+$</td>
<td>$+$</td>
<td>$-$</td>
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<tr>
<td>Small cell carcinoma</td>
<td>$+$</td>
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<td>$-$</td>
<td>$-$</td>
<td>$-$</td>
<td>$+$</td>
<td>$+$</td>
<td>$-$</td>
</tr>
<tr>
<td>Hematopoietic malignancies</td>
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<td>$-$</td>
<td>$-$</td>
<td>$-$</td>
<td>$-$</td>
<td>$+$</td>
<td>$+$</td>
<td>$-$</td>
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<tr>
<td>Melanoma</td>
<td>$-$</td>
<td>$-$</td>
<td>$-$</td>
<td>$-$</td>
<td>$-$</td>
<td>$+$</td>
<td>$+$</td>
<td>$-$</td>
</tr>
</tbody>
</table>

* CK indicates cytokeratin; $\approx$, variable; $-$, negative; and $+$, positive.
† Often negative but occasionally positive.
‡ Nonspecific cytoplasmic immunoreactivity.
§ Cytokeratin positive in $\approx$50%, epithelial membrane antigen positive in $\approx$100%.
|| Positive in cartilaginous areas.
¶ Positive only in rhabdomyomatous Wilms tumor.
# Positive only in schwannian stroma.
** Frequently negative in lymphoblastic lymphoma.
†† Positive in most lymphoblastic lymphomas.

**recognized usefulness of screening markers in characterization of undifferentiated malignant neoplasms.**

### SMALL ROUND CELL TUMORS

Small round cell tumors comprise heterogeneous neoplasms composed of relatively small, round to oval, closely packed undifferentiated cells with high nuclear-cytoplasmatic ratio, scant cytoplasm, and round nuclei with evenly distributed, slightly coarse chromatin, and small or inconspicuous nucleoli. In spite of a similar light microscopic morphology, SRCTs include pathologic entities from vastly different lineages, including (1) epithelial tumors, for example, small cell carcinoma (SmCC) (poorly differentiated neuroendocrine carcinoma); (2) mesenchymal tumors encompassing malignant solid neoplasms of childhood and other small round cell sarcomas; and (3) tumors with overlapping features, such as lymphoma and melanoma. Because of similar routine light microscopic features of these tumors, immunohistochemistry is often mandated for a definitive diagnosis. The immunoprofile of SRCTs is provided in the following and in Table 2, and an algorithmic immunohistochemical analysis is outlined in Figure 4.

**Ewing Sarcoma/Primitive Neuroectodermal Tumor**

CD99, the product of the MIC2 gene, is a cell surface glycoprotein that is expressed in more than 95% of Ewing sarcoma/primitive neuroectodermal tumors (EWS/PNETs) with a diffuse membranous staining pattern. CD99, however, is also expressed in several other SRCTs including lymphoblastic lymphoma (up to 90%), acute myelogenous leukemia (43%), granulocytic sarcoma (55%), small cell variant of poorly differentiated synovial sarcoma (PDSS) (nearly all), mesenchymal chondrosarcoma (80%–100%), desmoplastic small round cell tumor (DSRCT) (up to 50%), and rarely in rhabdomyosarcoma (RMS). CD99, however, is not expressed in neuroblastoma and is only exceptionally present in blastema-rich nephroblastoma. In contrast, CD56, a neural cell adhesion molecule (NCAM), which is positive in most SRCTs, is expressed in only 10% to 25% of EWS/PNETs and rarely in lymphoblastic lymphoma (<10%). Therefore, a CD99+/CD56– profile supports the diagnosis of EWS/PNET or lymphoblastic lymphoma against other SRCTs.

The characteristic translocation in EWS/PNET, t(11;
differentiation. Although a nuclear staining is deemed as the absence of reactivity for Myo-D1 and myogenin, differentiated nonspecific. Because of the potential for cytoplasmic staining for WT1, not the specific markers for RMSs, are not specific for these tumors regardless of morphologic evidence of skeletal muscle differentiation. These tumors are characterized by a polyphenotypic immunoprofile of mesenchymal chondrosarcoma includes variable expression for NSE and desmin but negative staining for CKs and myogenin. CD99 is demonstrated in most cases (80%–100%) in the small cell component. The small cell variant is often difficult to distinguish from other SRCTs, in particular EWS/PNET. The distinction between Ewing sarcoma (EWS) and EWS/PNET by positive staining for EMA (95%–100% of cases), CK (~50%), CD56 (100%), and collagen IV (100%). These markers are conversely negative in most EWS/PNETs. Because synovial sarcoma is nearly always negative for CD34, a positive stain for CD34 essentially excludes the diagnosis of PDSS. Most synovial sarcomas regardless of histology have the specific translocation t(X;18)(SYT-SSX); hence, in questionable cases molecular testing may be required for definitive diagnosis.

Mesenchymal Chondrosarcoma

Mesenchymal chondrosarcoma is a biphasic tumor composed of highly undifferentiated small round cells, admixed with islands of hyaline-like cartilage. If the histologic tissue includes only the undifferentiated small cell component, the distinction of mesenchymal chondrosarcoma from other SRCTs especially EWS/PNET will be difficult or perhaps impossible. Although the cartilaginous areas are reactive for S100 protein, the small cell component is typically not. The immunoprofile of mesenchymal chondrosarcoma includes variable expression for NSE and desmin but negative staining for CKs and myogenin. CD99 is demonstrated in most cases (80%–100%) in the small cell component.

Small Cell Osteosarcoma

Because of the lack of a specific immunoprofile for osteosarcoma, recognition of the small cell variant of osteosarcoma from other SRCTs essentially relies on the observation of osteoid production (Figure 7). Although monoclonal antibodies for osteocalcin are specific for osteoid-forming tumors, only a minority of small cell osteosarcoma show osteocalcin reactivity. Osteosarcomas are immunophenotypically heterogeneous and may occasionally express desmin, smooth muscle actin, S100 protein, and rarely CK, creating a potential diagnostic pitfall in their distinction from other SRCTs.

Wilms Tumor

Wilms tumor is classically a triphasic tumor composed of blastemal, epithelial, and stromal elements, but on occasions, particularly in small biopsy materials, it may present as a monophasic lesion with only blastemal compo-
Figure 6.  Photomicrograph of desmoplastic small round cell tumor (hematoxylin-eosin, original magnifications ×10 [a] and ×20 [b]), showing coexpression of cytokeratin (original magnification ×20 [c]) and desmin (original magnification ×20 [d]).

Figure 7.  Photomicrograph of small cell osteosarcoma recognized by lacelike osteoid closely associated with tumor cells (hematoxylin-eosin, original magnification ×20).

Figure 8.  Photomicrograph of Merkel cell carcinoma showing positive staining for CK20 with a distinct paranuclear dotlike pattern (original magnification ×40).
nent. Blastaema-rich Wilms tumor, mainly composed of undifferentiated blastemal cells, may be difficult to distinguish from other SRCTs from a morphologic perspective, especially in the setting of metastatic disease.

WT1, the Wilms tumor suppressor gene, located on chromosome 11p13, encodes a putative transcription factor implicated in tumorigenesis and in normal urogenital development. WT1 nuclear staining in the blastemal area is seen in 70% to 100% of cases. Although the blastemal component is reactive for vimentin and desmin (partially in up to 90%), the absence of staining for myogenin and Myo-D1 discriminates blastemal Wilms tumor from RMS. Blastemal foci are either negative or only focally positive for CK. Although rare instances of CD99 expression have been reported, staining for FLI-1 has never been observed.

Neuroblastoma

Neuroblastoma is characterized by a neuronal phenotype, which is demonstrated by several markers including NSE (positive in 38%–95%), neurofilament (63%), CD56 (NCAM) (100%), synaptophysin (65%–88%), and chromogranin (60%–88%). Expression of the more specific neuroendocrine markers, including chromogranin and synaptophysin, may diminish in less differentiated tumors.

The following markers, which are negative in neuroblastoma, can help differentiate this tumor from EWS/ PNET (CD99+), SmCC (CK+), lymphoma (CD45+), melanoma (S100+), and RMS (positive myogenous markers). Because up to 33% of olfactory neuroblastomas may be CK positive, a concomitant negative EMA may help differentiate them from SmCC. Although the tumor cells are negative for S100 protein, the presence of S100-positive dendritic cells around lobules of tumor cells is a helpful immunohistochemical feature.

Small Cell Carcinoma

Small cell carcinomas (poorly differentiated neuroendocrine carcinomas) represent poorly differentiated neuroendocrine neoplasms with an epithelial lineage. They may originate from a variety of locations, most commonly the lung but also from extrapulmonary sites, including nasal cavity and paranasal sinuses, breast, uterine cervix, bladder, prostate, gastrointestinal tract, pancreas, thyroid, adrenal gland, skin (Merkel cell carcinoma), and salivary glands. The histopathologic features of these tumors, regardless of the site of origin, are nearly identical.

The immunodiagnosis of SmCCs rests on the immunohistochemical proof of a simultaneous epithelial and neuroendocrine differentiation. The former is reflected by reactivity for keratin, especially LMW CKs (CK8 and CK18), and the latter by a positive neuroendocrine panel, which in order of increasing specificity includes NSE, CD56 (NCAM), synaptophysin, and chromogranin. Against a common histologic and immunohistochemical background, SmCC from different organs may display additional immunophenotypes that help discriminate the primary site, because not infrequently these tumors present as metastases of unknown origin. For example, among SmCCs from different sites, including gastrointestinal origin, CK20 is positive only in Merkel cell carcinomas (≥97%) and salivary gland SmCCs (≤60%) often with a distinct paranuclear punctate pattern (Figure 8). Another example is positive reaction for estrogen receptor (ER) and progesterone receptor (PR), which is seen in two thirds of mammary SmCCs according to 1 report. Although immunoreactivity for steroid hormone receptors, especially PR, has been occasionally observed in neuroendocrine tumors from various primary sites, unlike breast, simultaneous expression of ER and PR is unusual for them. Thyroid transcription factor 1 (TTF-1) is a sensitive marker for lung SmCC (positive in 80%–100%); however, TTF-1 expression has been also observed in various extrapulmonary SmCCs in several settings (11%–80%). TTF-1, therefore, should not be considered as a sole determinant in distinguishing extrapulmonary SmCC from its pulmonary counterpart. TTF-1 expression, however, is consistently negative in Merkel cell carcinoma.

One distinctive example of organ-specific SmCC is that from the ovary. There are 2 distinct types of ovarian SmCC. One is the neuroendocrine type, which is morphologically and immunohistochemically indistinguishable from the pulmonary SmCC. The second is the hypercalcemic type, which has a distinctive immunoprofile, dissimilar to that of traditional SmCC, characterized by positive reactivity for CK, calretinin, CD10, N-terminal of WT1, p53, and occasionally parathyroid hormone; negative staining for chromogranin, CD99, desmin, inhibin, S100, and TTF-1; and variable reaction for other neuroendocrine markers.

One should be aware that extrapulmonary SmCCs do not consistently express the specific antigens of the organs of their origin. For instance, SmCCs of the prostate are negative for prostate-specific antigen (PSA) and prostate acid phosphatase (PAP), and those of the urinary bladder are negative for thrombomodulin, uroplakin III, high-molecular-weight cytotkeratin (HMW CK), and CK20. A positive CDX2, although specific to tumors of intestinal origin, is seen in only 20% of SmCCs of the colon.

Sinonasal undifferentiated carcinoma, a rare, highly aggressive tumor type arising in the nasal cavity and paranasal sinuses, should be considered in the differential diagnosis of both SRCTs and undifferentiated large carcinomas in the head and neck region. These tumors are generally positive for CKs but exclusively for CKs of simple epithelia, such as CK8 (100%), CK19 (50%), and CK7 (50%), and as such are negative for CK5/6. They stain variably for EMA (18%), NSE (18%), and CD99 (14%) but are typically negative for chromogranin and synaptophysin.

Hematopoietic Malignancies

A dense infiltrate of relatively small undifferentiated cells of uncertain origin may be the first presentation of a hematolymphoid malignancy. As stated previously, because lymphoblastic lymphomas may not express CD45, a negative CD45 (LCA) does not totally exclude the possibility of hematopoietic malignancies. Nuclear staining for terminal deoxyribonucleotide transferase (TdT), which is a sensitive marker for both T- and B-precursor lymphoid cells, on the other hand, is considered the hallmark of lymphoblastic lymphoma. The majority (85%–90%) of lymphoblastic lymphomas derive from precursor T cells, and the rest originate from immature B cells. CD43 is a sensitive, although not a specific, T-cell marker. Cytoplasmic CD3 (not surface CD3) is also frequently expressed by T-precursor lymphoblasts. CD79a is a more sensitive marker for detection of immature B cells.
Table 3. Tumor-Specific Markers and Their Staining Pattern*

<table>
<thead>
<tr>
<th>Marker</th>
<th>Tumor</th>
<th>Staining Pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTF-1</td>
<td>Lung, thyroid</td>
<td>Nuclear</td>
</tr>
<tr>
<td>Thyreoglobulin</td>
<td>Thyroid</td>
<td>Cytoplasmic</td>
</tr>
<tr>
<td>HepPar-1</td>
<td>Hepatocellular</td>
<td>Cytoplasmic</td>
</tr>
<tr>
<td>CDX2</td>
<td>Colorectal/duodenal</td>
<td>Nuclear</td>
</tr>
<tr>
<td>Villin</td>
<td>Gastrointestinal (epithelia with brush border)</td>
<td>Apical</td>
</tr>
<tr>
<td>ER/PR</td>
<td>Breast, ovary, endometrium</td>
<td>Nuclear</td>
</tr>
<tr>
<td>GCDFP-15</td>
<td>Breast</td>
<td>Cytoplasmic</td>
</tr>
<tr>
<td>Mammaglobin</td>
<td>Breast</td>
<td>Cytoplasmic</td>
</tr>
<tr>
<td>RCC marker</td>
<td>Renal</td>
<td>Membranous</td>
</tr>
<tr>
<td>PSA</td>
<td>Prostate</td>
<td>Cytoplasmic</td>
</tr>
<tr>
<td>PAP</td>
<td>Prostate</td>
<td>Membranous</td>
</tr>
<tr>
<td>Uroplakin III</td>
<td>Urothelial</td>
<td>Nuclear or cytoplasmic</td>
</tr>
<tr>
<td>Inhibin</td>
<td>Sex cord–stromal, adenocortical</td>
<td>Cytoplasmic</td>
</tr>
<tr>
<td>Melan-A</td>
<td>Adrenocortical, melanoma</td>
<td>Cytoplasmic</td>
</tr>
<tr>
<td>Calretinin</td>
<td>Mesothelioma, sex cord–stromal, adenocortical</td>
<td>Nuclear or cytoplasmic</td>
</tr>
<tr>
<td>WT1</td>
<td>Ovarian serous, mesothelioma, Wilms, desmoplastic small round cell</td>
<td>Nuclear</td>
</tr>
<tr>
<td>Mesothelin</td>
<td>Mesothelioma</td>
<td>Cytoplasmic/membranous</td>
</tr>
<tr>
<td>D2-40</td>
<td>Mesothelioma, lymphatic endothelial cell marker</td>
<td>Membranous</td>
</tr>
</tbody>
</table>

* TTF-1 indicates thyroid transcription factor 1; HepPar-1, hepatocyte paraffin 1; ER/PR, estrogen receptor/progesterone receptor; GCDFP-15, gross cystic disease fluid protein 15; RCC, renal cell carcinoma; PSA, prostate-specific antigen; and PAP, prostate acid phosphatase.

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Compared with CD20. Thus, if lymphoblastic lymphoma is suspected, the panel should include TdT, CD43, and CD79a, in addition to CD45.

Myeloid (granulocytic) sarcomas with little or no evidence of myeloid differentiation may manifest as undifferentiated tumors, sometimes with small round cell morphology. A high index of suspicion is often required to avoid diagnostic overlook of these malignancies. Myeloblasts are usually positive for CD45 (in 75% of cases), CD43 (100%), myeloperoxidase (variably), and lysozyme (variably) but are generally negative for B- and T-lineage markers, including CD79a and CD3, respectively. As mentioned previously, most lymphoblastic lymphomas and a large fraction of myeloid sarcomas express CD99. However, application of lymphoid markers usually helps to distinguish hematolymphoid malignancies from Ewing sarcomas, which are negative for these markers.

**Malignant Melanoma**

In keeping with various cytomorphologic and architectural manifestations of malignant melanoma (MM), its small cell (neuroendocrine-like) variant, which occurs more commonly within the nasal cavity and paranasal sinuses, is a differential diagnostic consideration for SRCTs. Because melanoma with small cell morphology often lacks melanin pigment, immunohistochemistry plays an important role in its recognition.

The immunoprofile of MM is discussed in more detail later in the section on tumors with overlapping histologic features. Herein the potential for expression of aberrant markers in small cell melanoma as a source of diagnostic confusion with other SRCTs is highlighted. These include CD99 in rare to up to 60% of cases, WT1 (cytoplasmic but not nuclear pattern) in as many as 70%, CD10 in 40% to 50%, CD68 (a histiocytic marker) in 86%, NSE in approximately 50%, and neuroendocrine markers (CD56, CD57, and synaptophysin) in up to 13%. Chromogranin, on the other hand, is consistently absent in melanocytic tumors.

**UNDIFFERENTIATED “CARCINOMATOUS” TUMORS**

Undifferentiated tumors with a carcinomatous appearance are characterized by large round-oval to polygonal cells with a nesting arrangement. These histologic attributes, however, are not specific to carcinomas and may be mimicked by other tumors, including sarcomas with epithelioid appearance, melanoma, and hematopoietic malignancies. Screening panel for major lineage determination (see previous discussion) is essential for clarification of the true identity of these tumors.

**Tissue- or Organ-Specific Determination**

Once the diagnosis of carcinoma by broad lineage markers is established, immunohistochemistry may assist further by delineation of the cell line of differentiation. This is achieved by analysis of CK subtypes and other complementary or tissue- or organ-specific markers (Table 3). Although some markers are expressed almost exclusively in a specific tissue, for example, PSA and PAP for prostate and uroplakin III for urothelial epithelium, others are not strictly organ or tissue specific but may help focus the diagnosis to a specific area.

It should be mentioned that because most reports on the sensitivity and specificity of markers in the literature are derived from studies that encompassed primary and metastatic tumors of various grades, it is difficult to extrapolate those parameters exclusively in respect to undifferentiated or poorly differentiated forms of tumors. Nevertheless it can be concluded from the literature that for most entities, the sensitivity of tissue-specific markers declines as the tumor grade increases. Also, although the antigenic expression of some markers appears to be robust during metastasis, for example, CDX2 for colorectal carcinoma, others, such as the renal cell carcinoma (RCC) marker, tend to reduce their sensitivity in metastatic sites.

**CK Profile.**—The CK phenotype often provides helpful clues in determination of the cell line of differentiation in both primary and metastatic carcinomas. This reflects the observation that tumors tend to recapitulate the CK profile of the normal cells from which they are derived. Although metastatic tumors may gain or lose antigens compared with primary tumors, their CK profiles usually remain the same, as demonstrated by a number of studies, including a comprehensive study of CK7 and CK20 for 384 primary tumors and their metastasis and other studies focusing on CK20 expression by primary and metastatic colorectal...
### Carcinomatous tumors

Broad spectrum CKs+ S100–, HMB45– CD45–

<table>
<thead>
<tr>
<th>CK7+/CK20+</th>
<th>CK7+/CK20−</th>
<th>CK7−/CK20+</th>
<th>CK7−/CK20−</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urothelial CA</td>
<td>Breast CA</td>
<td>Lung SmCC (majority)</td>
<td>Prostate adenoCA</td>
</tr>
<tr>
<td>uroplakin+</td>
<td>ER/PR+</td>
<td>TTF-1+</td>
<td>PSA+</td>
</tr>
<tr>
<td>thrombomodulin+</td>
<td>GCDFP+</td>
<td>NE markers+</td>
<td>PAP+</td>
</tr>
<tr>
<td>P63+</td>
<td>mammaglobin+</td>
<td>p63−</td>
<td>CEA−</td>
</tr>
<tr>
<td>CK5/6 (−1/2+)</td>
<td>CEA+</td>
<td>Mesothelioma (−2/3)</td>
<td>uroplakin−</td>
</tr>
<tr>
<td>Pancreatic adenoCA (−2/3)</td>
<td>Endometrial adenoCA</td>
<td>WT1+</td>
<td>OCT3/4 positive</td>
</tr>
<tr>
<td>CEAX</td>
<td>vimentin+</td>
<td>CK5/6−</td>
<td>OCT3/4</td>
</tr>
<tr>
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<td>ER/PR+</td>
<td>CK5/6−</td>
<td>OCT3/4+</td>
</tr>
<tr>
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<td>CEA−</td>
<td>OCT3/4</td>
<td>CD30+</td>
</tr>
<tr>
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<td>Endocervical adenoCA</td>
<td>OCT3/4</td>
<td>OCT3/4</td>
</tr>
<tr>
<td>CDX2 (variable)</td>
<td>CEA+</td>
<td>OCT3/4</td>
<td>OCT3/4</td>
</tr>
<tr>
<td>Ovarian mucinous CA</td>
<td>vimentin−</td>
<td>mesothelin+</td>
<td>OCT3/4</td>
</tr>
<tr>
<td>MUC5-AC+</td>
<td>−</td>
<td>CEA−</td>
<td>OCT3/4</td>
</tr>
<tr>
<td>MUC-2−</td>
<td>−</td>
<td>OCT3/4</td>
<td>OCT3/4</td>
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<td>OCT3/4</td>
<td>OCT3/4</td>
</tr>
<tr>
<td>AdenoCA of bladder</td>
<td>−</td>
<td>OCT3/4</td>
<td>OCT3/4</td>
</tr>
<tr>
<td>thrombomodulin+</td>
<td>−</td>
<td>OCT3/4</td>
<td>OCT3/4</td>
</tr>
<tr>
<td>CDX2 (variable)</td>
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<td>OCT3/4</td>
<td>OCT3/4</td>
</tr>
<tr>
<td>Gastric adenoCA (subset)</td>
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<td>OCT3/4</td>
</tr>
<tr>
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<td>−</td>
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<td>OCT3/4</td>
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</table>

Study Figure 9. Algorithmic immunohistochemical analysis of undifferentiated carcinomas. CA indicates carcinoma; adenoCA, adenocarcinoma; SmCC, small cell carcinoma; SCC, squamous cell carcinoma; RCC, renal cell carcinoma; HCC, hepatocellular carcinoma; ¶, seminoma is keratin negative, OCT3/4 positive; *NE markers, neuroendocrine markers, including synaptophysin, chromogranin, and CD56; †, undifferentiated anaplastic thyroid carcinoma is often negative for thyroid transcription factor 1 (TTF-1) and thyroglobulin; and ‡, characteristic canalicular pattern.

Coordinate expression of CK7 and CK20 defines subsets of carcinomas, as shown in Figure 9. The CK7/CK20 phenotype can be especially useful in certain clinical situations, including the differentiation between prostate (CK7+/CK20+) and urothelial (CK7+/CK20 variable) carcinoma (Figure 10); poorly differentiated squamous (CK7+) and poorly differentiated urothelial (CK7+) carcinoma of the urinary bladder; and metastatic colorectal carcinoma (CK7+/CK20+) from primary nonmucinous ovarian carcinoma or primary endometrial, pulmonary, or mammary adenocarcinoma (CK7+/CK20+).122,124

Other CK subtypes may also have a role in defining the lineage of tumor; for example, CK19 combined with CK7 helps to differentiate between hepatocellular carcinoma (HCC) (CK7−/CK19+) and bile duct carcinoma (CK7+/CK19−).
Figure 10. Photomicrograph of urothelial carcinoma with positive staining for cytokeratin (CK) 7 (a) and CK20 (b) (original magnifications ×20).

Figure 11. Photomicrograph of lung adenocarcinoma with diffuse nuclear staining for thyroid transcription factor 1 (original magnification ×10).

Figure 12. Photomicrograph of epithelioid mesothelioma with nuclear and cytoplasmic staining for calretinin (original magnification ×20).

Figure 13. Photomicrograph of seminoma, showing a diffuse strong nuclear staining for OCT3/4 (original magnification ×20).

Figure 14. Photomicrograph of sarcomatoid carcinoma with cytokeratin expression in both sarcomatous and carcinomatous areas (original magnification ×20).
Carcinoembryonic antigen (CEA) is a nuclear oncofetal glycoprotein. Carcinoembryonic antigen is predictive of a squamous origin. Because urothelial carcinoma also expresses p63 (in 70%–95% of cases) and, in addition to CK5/6, is recognized as a specific monoclonal antibody, have cross reactivity with biliary glycoprotein antigen. Carcinoembryonic antigen is also frequently used as a negative marker in the mesothelioma panel.

**MOC-31.** MOC-31 is a cell surface glycoprotein largely found on the epithelial cells. MOC-31 helps differentiate between adenocarcinoma (MOC-31 positive) and mesothelioma (MOC-31 negative). MOC-31 is also useful in the recognition of cholangiocarcinoma and other metastatic adenocarcinomas (MOC-31 positive) from solid areas of ovarian serous adenocarcinoma (MOC-31 negative).

**p63.** p63, a p53 homologue, is a marker for basal cells and helps maintain basal cells in squamous and other epithelial linings. p63 stains the vast majority of SCCs (~97%) and, in addition to CK5/6, is recognized as a good marker for SCC, especially the poorly differentiated forms. Thus, a combined p63+/CK5/6+ immunoprofile in a poorly undifferentiated carcinoma is highly predictive of a squamous origin. Because urothelial carcinoma also expresses p63 (in 70%–95% of cases) and CK5/6 (50%–63%), a p63+/CK5/6+ immunoprofile could also suggest a urothelial carcinoma. The 2 entities are nevertheless distinguished based on their different coordinate CK7/CK20. p63 expression in the lung, however, is not specific to SCC; thus, a subset of adenocarcinomas (30%) and large cell carcinomas (37%), 50% of large cell neuroendocrine carcinomas (particularly higher-grade tumors), and a variable proportion of SmCCs (6%–77%) stain for p63. Because p63 is consistently negative in mesothelioma, it can assist in differentiating SCC of the lung from epithelial mesothelioma.

**Neuroendocrine Markers.** Neuroendocrine markers are tissue indicators of neuroendocrine neoplasms, including those with epithelial lineage (neuroendocrine carcinomas) and those with neural derivation, such as paraganglioma/pheochromocytoma and neuroblastoma.

The 2 most reliable markers of neuroendocrine neoplasms, synaptophysin and chromogranin, have a comparable sensitivity; thus, they are always used together as complementary reagents for neuroendocrine lineage determination. CD56 is generally regarded as a broad-spectrum neuroendocrine marker and perhaps the most sensitive and is instrumental in confirming the diagnosis of neuroendocrine tumors in small biopsies. CD56, however, is not specific for neuroendocrine delineation because it may label occasional nonneuroendocrine tissues and their malignant counterpart (e.g., follicular and papillary thyroid, renal cell, and hepatocellular carcinoma), natural killer cells, some T-cell lymphomas, and a large number of SRCTs.

Neuron-specific enolase suffers a poor specificity for neuroendocrine tumors, and, as such, it is not used as a sole determinant of neuroendocrine differentiation.

An undifferentiated carcinoma may turn out to have an occult neuroendocrine differentiation, disclosed by immunostain. Although neuroendocrine markers are not usually included in the initial diagnostic panel for an undifferentiated tumor, detection of neuroendocrine differentiation is clinically significant, because this may imply prognosis and therapy similar to those for SmCC. Because positive staining in a few tumor cells is frequent in any undifferentiated carcinoma, the diagnosis of neuroendocrine carcinoma should only be made if the stain is unequivocal and, in our experience, present in at least 20% of the tumor cells.

In the lung, large cell neuroendocrine carcinoma must be differentiated from basaloid carcinoma. Because of their overlapping H&E morphology, the differential diagnosis is often difficult but can be facilitated by their specific immunoprofiles. Basaloid carcinoma is negative for neuroendocrine markers and TTF-1 and positive for HMW CK, whereas large cell neuroendocrine carcinoma is consistently positive for neuroendocrine markers, positive for TTF-1 in about 50% of cases, and often negative for HMW CK.

**Thyroid Transcription Factor 1.** TTF-1 is a nuclear transcription factor that promotes embryogenic pulmonary and thyroid differentiation and is expressed by most, but not all, lung or thyroid neoplasms. Although 80% to 100% of SmCCs and 96% to 100% of adenocarcinomas from lung express TTF-1 (Figure 11), pulmonary SCCs are negative in most cases.

Furthermore, TTF-1 expression tends to decrease in poorly differentiated (50% positive) compared with welldifferentiated (100% positive) adenocarcinomas, diminishing the sensitivity of this marker for identifying the pulmonary origin of a poorly differentiated adenocar-
cinoma. Among thyroid carcinomas, undifferentiated anaplastic thyroid carcinomas are unfaithful in terms of TTF-1 expression (positive in <5%). TTF-1, as mentioned previously, may also be expressed in SmCCs arising from a variety of locations other than the lung99,101,103,155 (see also “Small Cell Carcinoma”).

**Thyroglobulin.**—Thyroglobulin is a very specific marker for thyroid follicular and papillary carcinomas but only rarely stains cells in undifferentiated anaplastic thyroid carcinoma.154,156 Anaplastic thyroid carcinomas are generally positive for vimentin and CK157,158 but are negative for CEAA,157 TTF-1,154 and melanocytic, vascular, myogenous, and lymphoid markers.

**Hepatocyte Paraffin 1.**—Hepatocyte paraffin 1 (HepPar-1) is a monoclonal antibody that stains a cellular antigen of unknown function of normal hepatocytes and is known to be a highly sensitive (positive in >90% of cases) and relatively specific marker for HCC.159–164 HepPar-1 expression, however, decreases in HCC with higher nuclear grade.164 HepPar-1 is occasionally observed in nonhepatic carcinomas, including those of gastrointestinal origin, in particular gastric signet ring cell carcinoma (47%–83%), and rarely in other tumors.159,163–165

The distinction of HCC, especially its poorly differentiated forms, from metastatic adenocarcinoma and cholangiocarcinoma is commonly a diagnostic challenge. A panel that includes HepPar-1, MOC-31, pCEA, and CD10, in addition to CK7 and CK20, is often helpful in making the accurate diagnosis. The immunoprofile of HCC includes CK7+/CK20+, HepPar-1 positive, MOC-31 negative, sinusoidal cell CD34+, and a canalicular pattern of positive immunostaining with both pCEA and CD10.134,160,163,166 Metastatic adenocarcinoma and cholangiocarcinoma, on the other hand, are generally MOC-31 and CEAPositive, the latter with a membrane/cytoplasmic staining pattern. The canalicular staining pattern with antibodies to CD10, positive in 68% of HCC, is distinct from the membrane or cytoplasmic staining seen in RCC.166

**CDX2.**—CDX2, an intestine-specific transcription factor, is a sensitive and specific marker for colorectal and duodenal adenocarcinomas in both primary and metastatic sites.167–169 However, CDX2 expression tends to decline in the higher grade and stage of colorectal tumors (positive in only 56% of poorly differentiated tumors)169 and is practically absent in an undifferentiated subset of large cell colonic carcinoma, usually associated with DNA mismatch repair defects.170 CDX2 is variably expressed in other adenocarcinomas of the digestive tract, including gastric (55%–70%), esophageal (67%), pancreatic (32%–60%), and biliary (25%–60%).163,167

CDX2 is also observed in a few extraintestinal carcinomas. For example, 47% to 100% of primary adenocarcinomas of the bladder168,171 and 10.5% to 100% of ovarian carcinomas, particularly the mucinous type, are positive for CDX2.167–169 Because bladder adenocarcinoma also displays a “urothelial” profile (CK7, 65% positive; CK20, 53% positive; and thrombomodulin, 59% positive),172 it may be differentiated from metastatic colorectal carcinoma by immunohistochemistry.

**Villin.**—Villin is a cytoskeletal protein associated with brush border microvilli of the intestine and proximal renal tubular epithelium. Villin is a sensitive marker of gastrointestinal adenocarcinomas, staining 82% to 100% of primary and metastatic colonic adenocarcinomas.168,173,174 Villin expression does not seem to be associated with the state of tumor differentiation.173 Villin, however, also stains a number of extragastrointestinal adenocarcinomas, including some adenocarcinomas of ovary, endometrium, kidney, and bladder.171,173,175 Villin expression in lung adenocarcinoma correlates with the presence or absence of microvilli (positive in 67% and 10% of cases, respectively).174

**ER and PR.**—The role of ER and PR in determining the primary site in undifferentiated tumors is hampered by a wide spectrum of expression among a variety of tumors. Although ER and PR expression is expected to be associated with hormone-responsive organs and their neoplasms, such as breast, ovary, and endometrium,179 there are frequent examples of unexpected ER or PR expression reported in a variety of other tumors, including those from lung, thyroid, stomach,161 and some neuroendocrine tumors.97 Furthermore, given that many high-grade carcinomas arising from hormone-responsive organs such as breast lack ER expression, we discourage sole reliance on ER and PR as determinants of the site of tumor origin, except in selected differential diagnoses and in combination with other immunomarkers. An example of the utility of ER in a diagnostic panel is its application combined with CEA133 and vimentin in the distinction of an endometrial (vimentin+/ER-/CEA-) from an endocervical (vimentin+/ER-/CEA+) adenocarcinoma.

**Gross Cystic Disease Fluid Protein.**—Gross cystic disease fluid protein 15 (GCDFP-15), a 15-kd secretory glycoprotein of various body fluids, including saliva, milk, and seminal fluid, is considered a marker of apocrine differentiation182,183 with high specificity for breast carcinomas.134,136 In a study of 328 metastatic adenocarcinomas, Kaufmann et al184 demonstrated that expression of GCDFP-15 and/or ER or PR had a sensitivity of 83%, a specificity of 93%, and a predictive accuracy of 92% for carcinomas of the breast against all other carcinomas excluding ovarian carcinomas. In another study, including 105 breast cancers and 585 nonmammary malignancies, GCDFP-15 was able to identify breast carcinomas with a sensitivity of 74% and a specificity of 95%.185 Other tumor types with occasional GCDFP-15 expression include carcinomas of the salivary glands, sweat glands, and prostate.185,187 Although a very specific marker, GCDFP-15 is not a particularly sensitive marker of breast carcinoma.186,187 It is uncertain whether GCDFP-15 expression declines in poorly differentiated forms of mammary carcinoma.

**Mammaglobin.**—Mammaglobin, a mammary-specific member of the urotoglobin family, is overexpressed in human breast carcinoma. Mammaglobin expression has been observed in 48% to 84% of breast carcinoma and in 8% to 15% of carcinomas not from breast, including salivary gland tumors (55%) and endometrial carcinoma (13%).188–190 Although mammaglobin appears to be a more sensitive marker than GCDFP-15, it is not as specific as GCDFP-15 for breast carcinoma.188 The predictive value of a combined mammaglobin and GCDFP-15 panel for mammary carcinomas in tumors of unknown origin needs to be investigated.

**RCC Marker.**—Renal cell carcinoma marker, a monoclonal antibody against a normal human proximal tubular brush border glycoprotein known as gp200, decorates conventional and papillary RCCs with an approximate sensitivity of 85% and more than 95%, respectively.191,192 Among nonrenal carcinomas, a subset of breast (29%) and

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Thrombomodulin, a cell surface glycoprotein involved in the regulation of intravascular coagulation, is expressed in 70% to 90% of primary or metastatic urothelial carcinomas. It is also expressed by a variety of nonurothelial tumors, including SCC (majority) and endothelial vascular tumors. Thrombomodulin is additionally known as a positive mesothelioma marker, although not as specific or sensitive as the other markers discussed later.

Uroplakin III.—Uroplakin III, expressed by terminally differentiated superficial urothelial cells, is a highly specific marker for urothelial origin of tumors. This marker, however, is not quite sensitive for urothelial carcinomas; thus, it is expressed in up to 60% of urothelial carcinoma in primary sites and slightly less frequently in metastases (~50%).

The differential diagnosis between a poorly differentiated prostate adenocarcinoma involving the bladder and a high-grade urothelial carcinoma with prostatic extension can be very challenging. This challenge, which is usually solved by careful cytomorphologic evaluations (monotonous tumor cells, prominent nucleoli, and less mitoses for prostate cancers), may be facilitated by a panel that includes a number of discriminatory markers, in addition to CK profile, including PSA and PAP, markers of prostate adenocarcinoma, and HMW CK, p63, uroplakin III, and thrombomodulin, markers that are expected to be positive in urothelial carcinoma.

Inhibin.—Inhibin is a peptide hormone produced by ovarian granulosa cells and testicular Sertoli cells. It serves as a sensitive and highly specific marker for ovarian and testicular sex cord–stromal tumors. Inhibin is also a sensitive marker for adrenal cortical neoplasms and reliably differentiates cortical from medullary adrenal tumors.

Melan-A.—Melan-A, a product of MART-I gene, is an antigen on melanoma cells that is recognized by the antibody A103. Although Melan-A is essentially used as a melanoma marker, it is also a sensitive marker for adrenal cortical neoplasms and similar to inhibin and calretinin, a specific marker in differentiating cortical from medullary adrenal tumors. Melan-A is additionally expressed by perivascular epithelioid cell tumors (PEComa).

Calretinin.—Calretinin is a good marker for malignant mesothelioma with a sensitivity approaching 100%. It is also quite specific for mesothelioma against adenocarcinomas, which are positive for it in only 8% to 11% of cases. Calretinin decorates both mesothelial cells and malignant mesothelioma with both nuclear and cytoplasmic staining. Calretinin additionally serves as a highly sensitive marker for sex cord–stromal tumors. It is, however, not as specific as inhibin in this respect because it also labels a fraction of ovarian epithelial neoplasms (22%). Like inhibin and Melan-A, calretinin also stains adrenal cortical neoplasms and discriminates them from adrenal medullary tumors.

Mesothelin.—Mesothelin is a cell surface antigen that is strongly expressed in normal mesothelial cells, mesotheliomas, and a number of other carcinomas. Although a highly sensitive marker for mesothelioma, mesothelin may also be present in approximately half of the lung adenocarcinomas, as such, it has limited value in discriminating between the 2 entities. Carcinomas with consistently strong exhibition for mesothelin include nonmucinous carcinomas of the ovary and adenocarcinomas of the pancreas and ampulla of Vater.

WT1.—WT1, in addition to its diagnostic utility for SRCTs (see “Small Round Cell Tumors”), is a sensitive marker for epithelioid mesothelioma, successfully discriminating it from adenocarcinoma. Another epithelial tumor strongly positive for WT1 is ovarian serous carcinoma, which is positive in nearly all cases including the high-grade forms. Because both peritoneal mesothelioma and ovarian serous carcinoma metastatic to the peritoneum express WT1, additional markers are needed for their differential diagnosis: A panel including calretinin, Ber-EP4, ER, and PR is helpful in differentiating mesothelioma (calretinin+/Ber-EP4+/ER+/PR+) from primary or metastatic serous ovarian carcinoma (calretinin+/Ber-EP4+/ER+/PR+).

Other Mesothelioma Markers.—Immunohistochemistry has a crucial role in the differential diagnosis between
malignant epithelioid mesothelioma and adenocarcinoma metastatic to the serous membranes. A number of discriminatory markers are available to facilitate this recognition. It is generally recommended to include at least 2 positive and 2 negative markers in the differential panel for mesothelioma.

Calretinin, WT1, and CK5/6 (discussed earlier) are established as highly reliable positive mesothelioma markers.228 Other positive markers include mesothelin and thrombomodulin (discussed earlier). In addition, D2-40,230 a lymphatic endothelial marker, and h-caldesmon,231 a specific marker for smooth muscle tumors, have recently been shown to be valuable in discriminating mesothelioma from lung adenocarcinoma. On the other hand, CEA, MOC-31, Ber-EP4, BG-8, and B72.3128,129 are accepted as reliable negative markers for discriminating epithelioid malignant mesothelioma from pulmonary adenocarcinoma.

CD5.—CD5 is a useful marker of primary thymic carcinomas, expressed in neoplastic epithelial cells of the thymic carcinoma but typically not in thymoma or other carcinomas involving the mediastinum.232–234 Of the 2 used clones of anti-CD5 antibody, clone CD5/54/B4 identifies 30% to 67% of thymic carcinomas.235,236 The other clone, NCL-CD5-4C7, although more sensitive for thymic carcinomas (45%–100% positive), also labels other neoplasms occasionally.233,235

Markers of GCTs.—Germ cell tumors sometimes present as undifferentiated metastatic carcinomas. Accurate recognition of these tumors is of utmost importance because of the available effective therapy. Placental alkaline phosphatase is consistently present in embryonal carcinoma and seminoma and variably in several other GCTs, including yolk sac tumor and choriocarcinoma.237,238 Placental alkaline phosphatase immunoreactivity, however, is not completely specific to GCTs, as it has been seen in some soft tissue tumors with known myogenic differentiation.239

OCT3/4, also known as POU5F1, is a transcription factor and a robust diagnostic marker for seminoma (Figure 13) and embryonal carcinoma in both primary and metastatic sites.240–242 Seminoma also stains consistently with D2-40. Yolk sac tumor does not express OCT3/4 but is positive for α-fetoprotein, albeit with a patchy staining pattern. Human chorionic gonadotropin is consistently expressed by syncytiotrophoblasts of choriocarcinomas.

UNDIFFERENTIATED “SARCOMATOUS” OR “SARCOMA-LIKE” TUMORS

In the approach to undifferentiated tumors with sarcomatous appearance, exclusion of nonmesenchymal neoplasms such as sarcomatoid carcinoma and sarcomatoid mesothelioma and other mimickers, for example, spindle cell melanoma or hematopoietic malignancies with sarcomatous feature, is essential. The distinction is usually attained by using the screening panel previously discussed in the introduction.

Undifferentiated High-Grade Sarcomas

Once the true sarcomatous nature of an undifferentiated tumor is established, investigation for a specific mode of differentiation, that is, neural, myogenous, lipomatous, or vascular lineage, should be implemented.

Fletcher243 demonstrated that among 159 neoplastic lesions initially diagnosed as pleomorphic sarcoma, 63% could be reclassified as specific types of sarcoma after implementing further studies, including combined immunohistochemistry and electron microscopy. Coindre et al244 showed that among 25 tumors initially diagnosed as retroperitoneal malignant fibrous histiocytoma (MFH), 17 could be reclassified as dedifferentiated liposarcoma by extensive sampling, combined with immunohistochemistry and comparative genomic hybridization. These distinctions are important above the academic interest in view of their variable prognostic implications.245

It is emphasized that ancillary tests do not replace proper tumor sampling, which often helps detect tumor foci with features suggestive of or diagnostic for a specific line of differentiation. According to the report of the International Chromosomes and Morphology (CHAMP) study group on 46 pleomorphic soft tissue sarcomas, it is unlikely that cytogenetic analysis, mainly because of the karyotype complexity of these tumors, can further improve their differential diagnostic subclassification.246

With the help of immunohistochemistry in conjunction with generous tumor sampling, a high-grade undifferentiated sarcoma can often be classified into one specific category of pleomorphic sarcomas, including pleomorphic leiomyosarcoma, pleomorphic RMS, pleomorphic and dedifferentiated liposarcoma, osteosarcoma, pleomorphic malignant peripheral nerve sheath tumor (MPNST), and PDSS.

The diagnosis of pleomorphic leiomyosarcoma requires demonstration of a positive reaction for smooth muscle markers, including smooth muscle actin, muscle-specific actin, desmin, calponin, and h-caldesmon,246,247 in the presence of at least focal supporting morphologic characteristics (eosinophilic spindle cells with vesicular blunt-ended nuclei arranged in a fascicular pattern). The expression of myoid markers in the pleomorphic areas, compared with the leiomyosarcomatous foci, is usually significantly reduced.248 Among myoid markers, h-caldesmon appears to be a promising reagent for specific smooth muscle differentiation that allows distinction of leiomyosarcomas from other tumors with smooth muscle–like differentiation, including myofibroblastic tumors.249,250 However, only 40% of pleomorphic leiomyosarcoma are labeled with this antibody.247

The immunoprofile of pleomorphic RMS includes expression of muscle-related antigens, that is, desmin, myoglobin, and actin,250 along with a diffuse reaction with at least one skeletal muscle–specific marker including myogenin and Myo-D1.251 The staining pattern for skeletal muscle markers in pleomorphic RMS is typically diffuse, which should be distinguished from focal staining seen in a variety of sarcomas with limited areas of rhabdomyomatous differentiation.

The diagnosis of liposarcomas, until a specific lipoblast marker is discovered, continues to be made essentially on the basis of the H&E light microscopy. Although normal fat cells are positive for S100, neoplastic adipocytes stain inconsistently.252 S100 labels lipoblasts in up to half of pleomorphic liposarcomas,253–255 but nonlipogenic areas only rarely stain with S100.253,254 The aP2 gene product (aP2 protein) has been suggested as a relatively specific marker for lipoblasts in all types of liposarcoma.256 This marker also stains brown fat cells but reportedly not beign adipocytes or cells of other mesenchymal or epithelial tumors.257 Because of the paucity of pertinent studies, the diagnostic value of this marker remains to be deter-
tained. Positive immunostainings for MDM2 and CDK4, which correlate with amplification of these genes in dedifferentiated liposarcomas, may help differentiate dedifferentiated liposarcomas from poorly differentiated sarcomas.258

The diagnosis of osteosarcoma is essentially rendered at the H&E light microscopic level by demonstration of bone or lacelike osteoid associated with malignant cells. Osteocalcin, which seems to specifically highlight the osteoid and the cytoplasm of osteoblasts (90%–100% specific),77,78 may be potentially helpful in the diagnosis of osteosarcoma in small biopsy material in the absence of recognizable osteoid. Notably, osteosarcomas can be immuno-reactive for actin and rarely for epithelial markers.

The diagnosis of pleomorphic MPNST is immunohistochemically supported by demonstration of nerve sheath differentiation by a number of neural markers including S100, Leu-7 (CD57), myelin basic protein, and protein gene product 9.5.259,260 The coexpression of these antigens is more reassuring for the diagnosis because none of them in isolation is specific for nerve sheath tumors.259 A focal staining for S100 is seen in most MPNSTs (50%–60%),259,261 yet many high-grade MPNSTs display a decreased or negative reactivity for S100 and CD57.262

The diagnosis of high-grade spindle cell variant of PDSS is supported by demonstration of positive reaction for EMA, keratin and its subsets (CK7 and CK19), Bcl-2 antigen, and CD99 or CD117 and negative staining for S100 and CD34. In questionable cases, molecular testing may be required for definitive diagnosis.

Pleomorphic MFH or undifferentiated high-grade pleomorphic sarcoma is a group of pleomorphic sarcomas that do not demonstrate a definitive line of differentiation even with the application of immunohistochemistry. Malignant fibrous histiocytoma is therefore a diagnosis of exclusion, which is made in the absence of reaction with any lineage-selective markers in a high-grade pleomorphic sarcoma. With current advances in diagnostic techniques, it is expected that the number of tumors diagnosed as MFH will be progressively smaller. Because a number of nonmesenchymal neoplasms may impart an MFH-like morphology, exclusion of these entities by immunohistochemistry is inevitable. Although keratin may stain a minor portion (up to 25%) of pleomorphic MFHs, the staining is often weak and focal.55,263,264 The tumor cells may be focally positive for smooth muscle actin or muscle-specific actin, but they are generally negative for desmin and S100. Rare desmin-positive cells in tumors with MFH-like morphology should not be regarded as evidence of myogenic differentiation.

Sarcoma-like Tumors

Sarcomatoid Carcinoma.—Sarcomatoid (spindle cell) carcinomas are a group of poorly to undifferentiated carcinomas that contain a component of spindle cell differentiation with or without differentiated heterologous elements, such as malignant cartilage, bone, or skeletal muscle.265,266 Some tumors are histologically biphasic with obvious sarcomatous and carcinomatous areas, whereas others may show no obvious epithelial areas despite generous sampling.265,266 In such instances, the sarcomatoid foci are hardly distinguishable from true sarcomas at the light microscopic level; therefore, immunohistochemistry plays a pivotal role in delineation of epithelial differentiation.

The tumor cells often coexpress CK (Figure 14) and vimentin.266,268–270 However, because of the varied and unpredictable CK immunoreactivity in sarcomatoid carcinomas, multiple epithelial markers, including EMA and various CK subtypes, such as pancytokeratin, HMW CK (CK34BE12 or CK5/6), and CK7, may be necessary to demonstrate epithelial differentiation.267,269,270 Evaluation of a number of alternative immunostains beyond the traditional epithelial markers (CKs and EMA) in the sarcomatoid carcinomas of the head and neck, lung, and urinary bladder showed some values in exposing the epithelial identity of tumors in that setting by adding p63 in the panel.271

Sarcomatoid Mesothelioma.—Immunohistochemistry has a limited role in the diagnosis of sarcomatoid mesothelioma and its distinction from sarcomatoid carcinomas and sarcomas. Sarcomatoid mesothelioma shows a marked decline in the expression of epithelial and mesothelial markers and has a wide immunophenotypic overlap with sarcomas and sarcomatoid carcinomas.252–254 Only 57.8% of sarcomatoid mesotheliomas stain for calretinin, 39% for thrombomodulin, 25% for WT1, 19.6% for CK5/6, and 75% for keratin.272 On the other hand, up to 60% of them may stain for actin.259,273 It has been recently reported that a combination of calretinin and D2-40 improves the sensitivity for detecting mesothelioma in sarcomatoid areas to 66%.273 Nevertheless, because of the lack of a specific marker, the diagnosis of sarcomatoid mesothelioma should be made after exclusion of alternative diagnostic entities and only with an integration of clinical, radiographic, gross, microscopic, and immunohistochemical findings.

Spindle Cell MM.—When dealing with a malignant spindle cell tumor at any site, the possibility of spindle cell melanoma should always be considered. The sensitivity of S100 protein in spindle cell MM appears to be more or less similar to conventional MM,27 but HMB-45 expression is less frequent (positive in ~80% compared with 90%–100% in the conventional type).276 Of note, the immunohistologic features of desmoplastic MM, a morphologic subtype of spindle cell MM associated with pronounced desmoplasia, is substantially different from conventional melanoma and includes positive staining for S100 (in 94%) but lack of reactivity for HMB-45 or other melanoma-specific markers.277

TUMORS WITH OVERLAPPING HISTOLOGIC FEATURES

Tumors with nondonscript H&E histology that fail to fit into either a sarcoma or a carcinoma category often pose the greatest diagnostic challenge. The differential diagnosis is broad and includes melanoma, hematopoietic malignancies, neuroendocrine tumors, poorly differentiated carcinomas, and mesenchymal neoplasms with epithelioid appearance. Ancillary tests, including immunohistochemistry, play an essential role in the recognition of these tumors.

Sarcomas With Epithelioid Appearance

The screening panel can often successfully disclose the broad line of differentiation in tumors with overlapping histology (see “Broad Lineage Determination”). The epithelioid morphology of sarcomas, which commonly correlates with their potential CK expression, however, further complicates the distinction of these tumors from epithelial malignancies. In a proper setting, a vimentin+/
Figure 15. Algorithmic approach to undifferentiated tumors with overlapping histologic features. CKs indicate cytokeratins; SMA, smooth muscle actin; PDSS, poorly differentiated synovial sarcoma; MPNST, malignant peripheral nerve sheath tumor; and PEComa, perivascular epithelioid cell tumors.

CK+ or a coordinate vimentin+/CK+ in a tumor with overlapping histology should raise the possibility of sarcomas with epithelioid features and prompt performance of a battery of immunohistochemical stains for further characterization of these tumors (Figure 15). Sarcomas with epithelioid cells include epithelioid sarcoma, epithelioid angiosarcoma, clear cell sarcoma, epithelioid MPNST, and other rare sarcomas, such as sclerosing epithelioid fibrosarcoma, alveolar soft part sarcoma, and epithelioid leiomyosarcoma.

The immunoprofile of epithelioid sarcoma includes positive staining for vimentin (Figure 16, a), LMW CKs, and EMA and variable staining for CD34 (positive in 50%). The latter finding, if present (Figure 16, b), helps to distinguish epithelioid sarcoma from carcinomas, which are rarely CD34 positive.

Most epithelioid angiosarcomas are positive for both vimentin and CKs. These tumors are recognized by expression of at least one of the endothelial markers, including CD31, CD34, and factor VIII. FLI-1 protein has been recently shown to have equal or superior sensitivity and specificity compared with the traditional markers for vascular tumors.

Clear cell sarcoma has a similar immunohistochemical constituent to melanoma that includes expression of S100, HMB-45, and microphthalmia transcription factor in the majority of cases. It is, however, genetically different from melanoma by its specific t(12;22) translocation. Clear cell sarcomas are typically negative for CK and EMA.

Epithelioid MPNST, a rare variant of MPNST, may be recognized by positive staining for S100 (in 80%) and NSE. The epithelioid variant of pleomorphic liposarcomas in up to half of the cases may show reaction with S100 or epithelial markers, an important finding to be considered in the differential diagnosis of these tumors from solid carcinomas with clear cell feature. The diagnosis of a number of rare sarcomas with epithelioid appearance, for example, sclerosing epithelioid fibrosarcoma and alveolar soft part sarcoma, is essentially made on the basis of their distinct light microscopic features.

Miscellaneous Mesenchymal Tumors With Epithelioid Appearance

Some mesenchymal neoplasms of borderline or uncertain malignant behavior may impart epithelioid appearance and be considered in the differential diagnosis of undifferentiated carcinomas; a few examples of which are herein given. Perivascular epithelioid cell tumors are mesenchymal neoplasms of perivascular epithelioid cells, with a wide anatomic distribution, sometimes presenting as unusual clear cell tumors in various locations. Immunohistochemically, these tumors are characterized by coexpression of melanocytic, including HMB-45 and Melan-A, and smooth muscle markers. Sex cord–stromal tumors are a heterogeneous group of neoplasms of the ovary and testis with various histologic patterns, not uncommonly confused as an undifferentiated carcinoma. Epithelial membrane antigen, which is nearly always negative, is a more reliable marker in distinction of these tumors from epithelial neoplasms because sex cord–stromal tumors, in particular granulosa cell tumor, may variably stain for CKs (0%–64%). Both inhibin and calretinin are useful markers for confirming the diagnosis. Gastrointestinal stromal tumor, including the epithelioid subtype, is immunohistochemically characterized by expression of CD117 (c-Kit) and CD34 in most cases, rare expression of smooth muscle actin and desmin, and negative staining for S100.

Malignant Melanoma

S100 is a sensitive, albeit not a specific, melanoma marker, decorating more than 95% of MMs of primary and metastatic sites. The diagnosis of MM requires confirmation with a melanocytic-specific marker, including HMB-45, Melan-A, microphthalmia transcription factor, and tyrosinase.

HMB-45 is a specific monoclonal antibody against an antigen present in the cytoplasm of neoplastic melanocytic cells. It shows positive cytoplasmic staining in the majority of MMs (>95% in ethanol-fixed tissues and slightly less in formalin-fixed tissues), with the exception of des-
malignant melanomas, however, Melan-A seems to be more sensitive (positive in 82%) than HMB-45 (positive in 76%).219,221 Both HMB-45 and Melan-A stain the PEComa family of neoplasms,219,221 yet Melan-A also stains adrenal cortical neoplasms.220

Malignant melanomas stain intensely for vimentin but are typically negative for epithelial markers, glial fibrillary acidic protein, CD45, and desmin. However, aberrant expression for a number of immunostains, including CK, EMA, pCEA, or glial fibrillary acidic protein, has been rarely reported (also see "Malignant Melanoma" under "Small Round Cell Tumors").15,16,26,296

Hematopoietic Malignancies

The spectrum of hematolymphoid malignancies presenting as a mass of large atypical cells of uncertain origin is broad and includes various types of lymphoma, myeloid sarcoma, and plasma cell neoplasm, each with a diverse immunoprofile, the complexity of which is far beyond the scope of this manuscript. Some examples of the unexpected immunohistochemical expression in selected groups of hematopoietic tumors are herein provided.

As mentioned previously, CD45 (LCA) is a valuable tool in the diagnostic separation of hematopoietic neoplasms, particularly of the lymphoid type, from poorly differentiated epithelial and mesenchymal neoplasms. Non-Hodgkin lymphomas of the B- and T-cell types are immunoreactive for LCA in 93% to 100%.28,29 A negative LCA, however, does not absolutely preclude the diagnosis of lymphoma in a large cell undifferentiated tumor because LCA is rarely absent in some lymphomas of the T-cell type and some plasma cell neoplasms.

The immunoprofile of anaplastic large cell lymphoma is highly variable and includes a positive reaction for LCA (60%–70% of cases), CD30 (nearly all), T-cell markers (54%–70%), ALK protein (60%–85%), and EMA (~75%).18,297–299 Hence, a potential CD45+/EMA+ immunoprofile in anaplastic large cell lymphoma may pose diagnostic confusion with an undifferentiated carcinoma. On the other hand, the typical CK−/EMA+ immunoprofile in anaplastic large cell lymphoma may help to differentiate it from embryonal carcinoma (CK+/EMA−), which is also reactive for CD30.

Most but not all granulocytic sarcomas (~75%) express LCA.112 CD45 is a more sensitive marker for myeloid sarcomas, staining up to 100% of cases with an intense widespread staining pattern.112 The diagnosis of myeloid tumor, however, requires demonstration of more specific markers, including myeloperoxidase and lysozyme.

The immunoprofile complexity of neoplastic plasma cells (plasmacytoma or plasma cell myeloma), including variable expression for CD45, EMA, and CK, combined with commonly negative reaction for B-cell markers (CD19, CD20), may pose potential diagnostic pitfalls in their distinction from epithelial neoplasms.10,33,34 A high index of suspicion should direct to a panel that includes CD38, CD138, and κ and λ light chains. Of note, although...
In summary, classification of a tumor beyond its apparent undifferentiated morphology is possible in the majority of cases. This not only is important for prognostication and therapy but should also provide further insights into the pathobiology of these tumors. The diagnostic pathway is starting with recognizing a tumor as SRCT, carcinomatous tumor, sarcomatous (or sarcoma-like) tumor, or tumor with histologically overlapping features, followed by an immunohistochemical panel, which is judiciously constructed for each tumor. Awareness of the diagnostic utility of several tissue- or organ-specific immunomarkers, as summarized in this review, should help meet one of the most significant challenges in diagnostic pathology.

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