Pathology Update

THE ROLE OF IMMUNOHISTOCHEMISTRY IN THE DIAGNOSIS OF PRIMARY TUMORS OF THE BONE

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This regular feature presents special issues in oncologic pathology.

Introduction

Due to the rarity of primary bone tumors, few physicians accumulate enough experience in the diagnosis and treatment of these neoplasias. Clinical management is best achieved through a multidisciplinary approach in which surgeon, radiologist, medical oncologist, and pathologist combine their expertise to establish both an accurate diagnosis and a rational treatment plan. The diagnostic algorithm of a primary tumor of the bone is, and always has been, a collaborative effort in which clinical, radiologic, and pathologic features have to be considered. In the majority of cases, the pathologist can rely exclusively on histopathologic examination to provide an accurate diagnosis. In some cases, however, a variety of ancillary studies have to be employed to distinguish entities that share morphologic characteristics. Currently, immunohistochemistry has limited application in the differential diagnosis of primary bone tumors, but occasionally, characterization of the antigenic profile is the only way to properly classify a given neoplasm. Furthermore, immunohistochemical analysis is helping us to establish the histogenetic origin of many entities and to understand their pathogenesis.

The role of the pathologist in the management of bone tumors is essential. Accurate diagnosis of a given neoplasm determines not only the general patient’s prognosis but, more importantly, the type of therapeutic modality needed to achieve optimal results. Furthermore, new treatment protocols are constantly being developed, and it is the responsibility of the pathologist to properly classify a given tumor for successful inclusion in the appropriate protocol. When evaluating a bone tumor, however, the pathologist is confronted with several difficulties. Bone tumors are rare entities, and not all pathologists are exposed to bone pathology with the frequency needed to gain the necessary level of diagnostic confidence. Also, certain osseous tumors share histopathologic features and, in many cases, important diagnostic features may not be readily evident in small specimens. Finally, intramedullary lesions often must be decalcified, a process that may be associated with loss in cellular morphologic detail. All of these factors complicate the diagnostic process. Diagnosis for many entities can be reached by histopathology alone or can be interpreted in the context of clinicoradiologic findings, but for others, only a differential diagnosis can be reached without ancillary studies.

Electron microscopy can be extremely useful in the identification of certain histogenetic features such as epithelial, muscular, or neural differentiation. However, it is an expensive procedure that requires excellent technical preparations and sophisticated interpretation skills. Furthermore, electron microscopy is not widely available to the general pathologist, thus requiring the submission of the sample to an academic institution.

The same can be said for cytogenetics and for sophisticated molecular analysis. Molecular techniques, however, are rapidly becoming important components of the diagnostic armamentarium. In the last decade, the roles played by tumor suppressor genes, oncogenes, and cell cycle regulatory molecules in bone oncogenesis, differentiation, apoptosis, and multidrug resistance have been explored. Thus, bone tumors have been shown to be part of well-defined genetic syndromes such as Li-Fraumeni and Rothmund-Thompson, while the diagnostic significance of chromosomal translocations, gene fusions, and DNA repair mechanisms are beginning to be understood.1

Immunohistochemistry, however, is essential in identifying certain entities such as metastatic carcinomas and melanomas that can occasionally be confused, morphologically, with primary bone tumors. It is also routinely used to assign a phenotype to hematopoietic malignancies and to define histogenesis in morphologically related neoplasms such as the “small blue-cell” group of tumors. Several studies have shown that gentle decalcification methods preserve antigenicity relatively well for the most commonly used markers. Unfortunately, little is known about the antigenic specificity of normal bone tissue and bone neoplasias, and although several candidate antigens have been explored, reagents to detect bone-specific antigens are not yet available. The following is a review of the most commonly used markers and the antigenic profile of selected primary bone tumors and entities that are considered in the differential diagnosis.

Immunohistochemical Markers

Mesenchymal Marker

Vimentin -- Although of limited value in differential diagnosis, vimentin is an abundant antigen that can be demonstrated in most properly fixed tissues and survives most decalcification procedures. It is used, therefore, to assess antigen loss during processing. Thus, if vimentin is not expressed in a tissue sample that should express it, interpretation should be either done with caution or entirely avoided.

Epithelial Markers

Cytokeratins -- Cytokeratins are expressed in carcinomas and in the vast majority, if not all, of epithelial-like sarcomas (epithelioid and synovial sarcomas). Certain tumors express profiles of cytokeratin subsets that have been reported to be more or less specific, although this is rarely helpful in routine diagnosis.2

Epithelial Membrane Antigen -- Epithelial membrane antigen is expressed in approximately 75% of the epithelial-like sarcomas (epithelioid and synovial sarcomas) and in malignant peripheral nerve sheath tumors, leiomyosarcomas, histiocytes, and neoplasias of histiocytic origin, and in rare anaplastic lymphomas.3

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1. Fraumeni and Rothmund

2. Thompson

3. Cacho, MD, PhD
Neuronal, Nerve Sheath, and Melanocytic Markers

**S-100 Protein (S-100)** -- Widely distributed in peripheral and central nervous systems, the S-100 protein localizes to both the nucleus and the cytoplasm and, in the appropriate context, is one of the most useful markers. S-100 is expressed diffusely in neurofibromas and neurolemmomas, liposarcomas, ossifying fibromyxoid tumor, chondrosarcomas, and in 90% of clear-cell sarcomas, also known as melanomas of soft parts. Melanomas consistently express S-100, a feature that helps in the diagnosis of metastatic melanomas to the bone. Chondomas coexpress both S-100 and cytokeratin.

**Neurofilament Protein (NF)** -- Useful in the differential diagnosis of small round-cell tumors, NF is expressed by many neuroblastosas, medulloblastomas, retinoblastomas, primitive peripheral neuroepitheliomas and, focally, in rhabdomyosarcoma and in malignant fibrous histiocytoma.

**Leu-7 (CD57)** -- Although expressed in small round-cell tumors of childhood such as neuroblastoma, prominent expression in rhabdomyosarcoma limits its use in the differential of small round-cell tumors.

**Synaptophysin** -- Synaptophysin is expressed by tumors of neuronal origin including neuroblastoma, ganglioneuroblastoma, olfactory neuroblastoma, melanotic neuroectodermal tumor of infancy, peripheral neuroepitheliomas, and rare rhabdomyosarcomas.

**Neuron-Specific Enolase** -- Of limited use due to frequent, nonspecific, background staining, neuron-specific enolase is expressed in over half of neuroblastosas, one third of malignant melanomas, and a small percentage of nonneural tumors.

**Endothelial/Vascular Markers**

**CD31** -- Detection of the antigen gpIIa, the cellular adhesion molecule PECAM-1 (platelet endothelial cell adhesion), has been shown to be expressed in 80% to 100% of angiosarcomas and hemangiomas.

**CD34** -- A sensitive marker for endothelial differentiation, CD34 is expressed by 70% of angiosarcomas, 90% of Kaposi’s sarcomas, and 100% of epithelioid hemangioendotheliomas.

**Factor VIII Antigen (FVIII)** -- Restricted to endothelial cells and megakaryocytes, FVIII is less specific for endothelial neoplasms than are CD31 and CD34, although it is useful as a confirmatory marker (particularly in well-differentiated tumors).

**Fibrohistiocytic Markers**

**CD68** -- CD68 can be found in any tumor containing lysosomal granules or phagolysosomes. CD68 is expressed in only 50% of malignant fibrous histiocytoma cases and, given its nonspecificity, it should not be used as evidence of histiocytic lineage as initially reported.

**Miscellaneous Markers**

**MIC-2 Gene Product (CD99)** -- Located in the short arm of the sex chromosome, the MIC-2 gene product encodes a surface protein first described in T-cell and null-cell acute lymphoblastic leukemia. A recent antibody (HBA-71) detects an epitope present in Ewing’s sarcoma and peripheral neuroepitheliomas, alveolar rhabdomyosarcomas, ependymomas, and islet cell tumors.

**Alkaline Phosphatase, Osteonectin, Osteocalcin, and Collagens** -- These proteins have all been used as potential bone tissue markers. Although in certain conditions the expression of these markers may be helpful, their specificity remains in question and reagents are not readily available to most laboratories.

**Tumors**

**Bone-Forming Tumors**

Due to their central function in the process of mineralization, a group of proteins are considered to have some potential for tumor diagnosis: alkaline phosphatase, osteonectin, and osteocalcin. Osteocalcin is produced exclusively by bone-forming cells and therefore is receiving special attention as a specific marker. In the detection of bone-forming tumors, osteocalcin has been associated with 70% sensitivity and 100% specificity, compared with the 90% sensitivity and 54% specificity reported for osteonectin. At the present time, however, no specific marker is available to distinguish the bone matrix from its collagenous mimics.

**Osteoma, Osteoid Osteoma, Osteoblastoma** -- The diagnosis of these entities resides exclusively in morphologic features, and although a variety of lesions should be considered in the differential diagnosis, immunohistochemistry offers little help in the distinction. The nocturnal pain in osteoid osteoma, however, is mediated by prostaglandins, and it has been shown that in approximately 25% of osteoid osteomas, nerve fibers that express NF and S-100 are present in the reactive zone around the nidus and/or in the nidus itself. These fibers have not been observed in any other tumor, which suggests that the nerve supply of osteoid osteoma might serve as a marker in diagnostically difficult cases. Although occasionally observed in hematoxylin-eosin sections, NF and S-100 decorate the fibers and facilitate their detection.

**Osteosarcoma** -- The differential diagnosis of osteosarcoma from other sarcomas (eg, malignant fibrous histiocytoma, fibrosarcoma, Ewing’s sarcoma) is important because of the specific therapy available for osteosarcoma patients. Most osteosarcomas express vimentin and, according to some authors, some tumors focally express cytokeratin and desmin, although these findings have not been widely confirmed. Bone matrix proteins, such as osteocalcin, alkaline phosphatase, and osteonectin, are expressed in osteosarcomas. However, their presence has also been detected in chondrosarcomas, Ewing’s sarcoma, fibrosarcomas, and malignant fibrous histiocytomas. Caution should also be used in the interpretation of focal expression of a variety of markers (eg, S-100, actin, epithelial membrane antigen) found occasionally in otherwise typical osteosarcomas. Extraskeletal osteosarcomas of the fibroblastic subtype often have sparse amounts of osteoid and can be differentiated from malignant fibrous histiocytoma on the basis of strong expression of alkaline phosphatase. Chondroblastic osteosarcoma and chondrosarcoma, however, cannot be distinguished immunohistochemically. Furthermore, it remains to be seen if the expression of CD31 or CD34 helps in the differential diagnosis between telangiectatic osteosarcoma and angiosarcoma. The different types of collagen present in the bone matrix are also produced by other tumors and therefore have no application in differential diagnosis. However, recent reports suggest that the basic calponin gene, a smooth muscle differentiation-specific gene that encodes an actin-binding protein involved in the regulation of smooth muscle contractility, is expressed in osteosarcomas and that this expression may have favorable prognostic implications. The
A subtype of osteosarcoma that most likely will benefit from the application of an immunohistochemistry panel is the "small-cell" type. The diagnosis of this entity is difficult due to the paucity of osteoid and the similarity to other small round-cell tumors. Although the antigenic profile of small-cell osteosarcoma is unknown, expression of markers specific for other small-cell tumors help in ruling out this diagnosis.

**Cartilage-Forming Tumors**

Little is known about matrix biochemistry and cell differentiation in chondrogenic neoplasms. Normal chondrocytes typically express vimentin, S-100, and type II collagen. Neoplastic chondrocytes usually retain vimentin and S-100 expression, but little else is known about the expression of other antigens, and it is assumed that malignant cartilage-producing tumors have no specific antigenic profile. Although neoplastic chondrocytes in vitro can undergo full differentiation, the zonal expression of type X collagen is seen only in benign chondroblastomas. In enchondromas, the pattern of expression is more randomly distributed within the tumor; in chondrosarcomas, with spindle-shaped cells and noncartilaginous extracellular matrix, only focal expression is seen. Proliferative markers like c-erb B2 are not observed in either normal cartilage or chondromas but are frequently seen in chondrosarcomas, suggesting that they may be useful in predicting biological behavior.

**Osteochondroma, Periosteal Chondroma, Chondromyxoid Fibroma, Enchondroma** -- Immunohistochemistry has little or no value in the differential diagnosis of this group of tumors. Chondromyxoid fibroma is a rare benign bone tumor of uncertain histogenesis that expresses S-100, a finding consistent with the cartilaginous nature of the lesion and supporting its possible relation to chondroblastoma.

**Chondroblastoma** -- Chondroblastomas are unusual benign cartilage tumors of bone with well-defined histologic features. Chondroblasts express S-100, vimentin, and neuron-specific enolase and may show focal expression of osteonectin, cytokeratin, and epithelial membrane antigen. In approximately one third of the tumors, cytoplasmic expression of muscle-specific actin can be found in chondroblasts and chondrocytes. Moreover, these cells contain bundles of microfilaments with focal densities that are typical of myofilaments. Despite histogenetic considerations, immunohistochemistry helps in the distinction of chondroblastoma from other lesions that contain giant cells, such as giant-cell tumor and giant-cell reparative granuloma. These two entities do not express S-100, and their mononuclear population usually expresses histiocytic markers (e.g., α1-chymotrypsin, lysozyme) not expressed in chondroblastoma.

**Chondrosarcoma** -- Besides expression of S-100 and vimentin, chondrosarcomas may express Leu-7 and neuron-specific enolase. Although immunohistochemistry does not help in the distinction of chondrosarcoma from other cartilage-forming tumors, it is helpful in the distinction of chondrosarcoma from chondroma, which expresses epithelial membrane antigen, cytokeratins, and occasionally CEA. Expression of cytokeratins is also useful to distinguish metastatic carcinomas from clear-cell chondrosarcomas. In small biopsies containing exclusively the round-cell component of a mesenchymal chondrosarcoma, immunohistochemistry -- with an appropriate panel -- may reveal the true nature of the neoplastic cells and distinguish rhabdomyosarcoma, neuroendocrine carcinomat, and small round-cell tumor of childhood.

**Fibrous and Fibrohistiocytic Tumors**

**Fibrous Cortical Defect, Non-Ossifying Fibroma, Benign Fibrous Histiocytoma, and Desmoplastic Fibroma** -- Immunohistochemistry has little or no application in the differential diagnosis of these entities.

**Malignant Fibrous Histiocytoma (MFH)** -- The list of entities included in the differential diagnosis of MFH is extensive. Immunohistochemistry helps in the distinction of MFH (CD68+) from leiomyosarcoma (CD68–); MFH (S-100–) from malignant neurilemmoma (S-100+); and MFH (osteoclast–, alkaline phosphatase–) from fibroblastic osteosarcoma (occasionally positive for both). The distinction of cytokeratin-positive MFH from sarcomatoid carcinoma may be impossible by immunohistochemistry and is best accomplished by electron microscopy.

**Smooth Muscle Tumors**

**Leiomyosarcoma** -- Primary leiomyosarcoma of the bone is a rare tumor in an unusual location. The diagnosis requires (1) exclusion of leiomyosarcoma in other non-osseous locations and (2) intramedullary location of the epicenter of the tumor (more than 70% of the mass) with only limited extrasosseous extension. Osseous leiomyosarcomas frequently have the classic morphology, although epithelioid, myxoid, and pleomorphic variants can complicate the diagnosis. Expression of smooth muscle markers (smooth muscle actin, common muscle actin, and desmin) is consistently observed in the vast majority of tumors.

**Vascular Tumors**

**Angiosarcoma** -- Primary angiosarcoma of bone is a rare, high-grade sarcoma of vascular origin. The clinicopathologic, immunohistochemical, and ultrastructural features of angiosarcomas are not well defined. Angiosarcomas strongly express vimentin and, at least focally, factor VIII-related antigen. CD34 antigen is detected in 74% of cases and cytokeratins in 35% of cases. Epithelial membrane antigen, S-100 protein, and HMB45 generally are not expressed. Fifty-five percent of the tumors have intracytoplasmic aggregates of laminin. Alpha-smooth muscle actin is demonstrated in a pericytic pattern in 24% of the tumors. Tumors have poor prognosis if more than 10% of the cells express MIB-1, a proliferation marker.

**Lesions Containing Giant Cells**

In general, the osteoclasts and neoplastic giant cells of giant-cell tumor of bone and giant-cell reparative granuloma lack expression of HLA-DR (CD45), while giant cells of histiocytic origin and osteoclasts express CD68 and HLA-DR.

**Giant-Cell Tumor (GCT)** -- Although giant-cell tumor (GCT) of bone is a well-recognized neoplasm with distinctive clinical and histopathologic features, the histogenesis of the tumor cells, particularly of the mononuclear population, is still debated. GCT of bone is one of a few neoplasms in which macrophage/osteoclast precursor cells and osteoclast-like giant cells infiltrate the tumor mass. The gene transcripts of MCP-1, a monocyte chemo-attractant protein 1, are detected in all GCT and the protein is found in the cytoplasm of the stromal-like tumor cells of GCT of bone. This suggests that recruitment of CD68+ macrophage-like cells may be due to the production MCP-1 by stromal-like tumor cells. These CD68+ cells may originate from peripheral blood and could have the capability of further differentiating into osteoclasts within the tumor. However, the mononuclear stromal cells have been shown to express muscle actin (HHF35) and alpha-smooth muscle actin, while the osteoclast-like giant cells strongly coexpress muscle actin and CD68 but lack alpha-smooth muscle actin. These findings suggest a myofibroblastic origin. Therefore, the true histogenesis of the cell population, as well as the implications of these findings for GCT diagnosis in giant-cell tumors, remains unclear.

**Giant-Cell Reparative Granuloma** -- Giant-cell reparative granuloma (GCRG) is a reactive bone lesion that most often involves the jaws and, occasionally, the distal extremities. In extragnathic locations, GCRG may simulate other osteolytic giant cells lesions such as GCT of bone and aneurysmal bone cyst.
**Common Antigens Used in the Differential Diagnosis of Small Round-Cell Tumors**

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<th>Vimentin</th>
<th>Keratin</th>
<th>Desmin</th>
<th>NP</th>
<th>LCA</th>
<th>SSE-7</th>
<th>O13</th>
<th>S-100</th>
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<td>Osteosarcoma, small-cell type</td>
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<td>Chondrosarcoma</td>
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<td>Neuroblastoma</td>
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<td>Neuroendocrine carcinoma</td>
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<td>Rhabdomyosarcoma</td>
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<td>Lymphoma</td>
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<td>EWS/PNET</td>
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<tr>
<th>NF</th>
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<td>+</td>
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<td>Ewing’s sarcoma/peripheral neuroepithelioma</td>
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**Miscellaneous Tumors**

**Neuroectodermal Tumors of the Bone** -- “Small round-cell tumors” is a descriptive name given to members of a family of sarcomas with specific morphologic, biological, and clinical features (Table). The family includes Ewing’s sarcoma, rhabdomyosarcoma, small-cell osteosarcoma, mesenchymal chondrosarcoma, neuroblastoma, lymphoma, and the rare “primitive sarcoma of bone” that has a blastemic appearance and a polyphenotypic antigenic profile and is perhaps related to the desmoplastic small round tumor (see below).37 Among these neoplasias, the most common is Ewing’s sarcoma (EWS). Recently, however, EWS variants have been recognized, including atypical EWS, atypical EWS with endothelial features, large-cell EWS, and EWS with neuroectodermal differentiation, also called peripheral primitive neuroectodermal tumor of the bone (PNET) or neuroepithelioma of the bone. The EWS group is characterized by chromosomal translocations leading to EWS-ETS gene fusions. These hybrid genes express chimeric proteins that are thought to act as aberrant transcription factors. In particular, t(11;22)(q24;q12) or t(21;22)(q12;q11) chromosomal translocations fuse the EWS gene from 22q12 with either the FL11 gene on 11q24 or the ERG gene on 21q12.38 These tumors express vimentin and, occasionally, cytokeratin and glial fibrillary protein. Antigens related to neuroectodermal differentiation such as neuron-specific enolase, S-100, and Leu-7 can be demonstrated in many cases. The protein coded by the MIC-2 gene (CD99), detected by antibodies HBA 71, P 30/32, and O13, is reported to be present in over 95% of EWS/PNET and has been considered a useful marker for the diagnosis of EWS/PNET. However, some rhabdomyosarcomas, lymphomas, neuroendocrine carcinomas, and the small-cell component of mesenchymal chondrosarcomas have been found to express it.12,39-41

Another member of the family, the desmoplastic small round-cell tumor (DSRT), is a multiphenotypic primitive tumor characterized by massive reactive fibrosis surrounding nests of tumor cells. The t(11;22)(p13;q12) chromosomal translocation that defines DSRT produces a chimeric protein containing the potential transactivation domain of the EWS protein fused to zinc fingers 2-4 of the Wilms’ tumor suppressor gene and transcriptional repressor WT1. By analogy with other EWS fusion products, the EWS-WT1 chimera may encode a transcriptional activator whose target genes overlap with those repressed by WT1. The oncogenic fusion of EWS to WT1 in DSRT results in the induction of platelet-derived growth factor-A (PDGFA), a potent fibroblast growth factor that contributes to the characteristic reactive fibrosis associated with this unique tumor.42

Although EWS and PNET are considered opposite ends of the spectrum of presentations of a single disease, important differences have recently been observed between both entities. Thus, the pattern of expression of NF observed in EWS differs from that of PNET and is similar to that of undifferentiated neural tissues. Furthermore, neural growth factor receptors in EWS seem to be nonfunctional, suggesting that EWS maintains a primitive phenotype. On the other hand, human gastrin-releasing peptide (GRP) has been found in approximately half of PNET but only rarely in other primary small round-cell tumors. GRP is a known autocrine growth factor in small-cell lung cancer and other neuroendocrine tumors. Its expression in PNET provides further evidence for a neuroectodermal histogenesis of these tumors.42-44

**Chordoma** -- The morphologic features of chordomas, although characteristic in the typical tumor, can be difficult to distinguish from those of renal cell carcinoma, extraskeletal myxoid chondrosarcoma, signet-ring cell adenocarcinoma, and a variety of other clear-cell neoplasms. Expression of cytokeratin subsets is useful to differentiate chordomas from chordosarcomas. Thus, chordomas consistently express cytokeratins K8, K19, and nearly always K5, but not K7 and K20. Keratins, however, are never expressed by skeletal chordosarcomas, although K8, and to a lesser extent K19, can be expressed by extraskeletal myxoid chordosarcoma with chordoid features, a tumor that commonly enters in the differential diagnosis of chordoma. HBME-1, a monoclonal antibody recognizing an unknown antigen on mesothelial cells and neuroendocrine tumors, is strongly expressed by chordoma and skeletal chordosarcoma but is almost never expressed in renal or colorectal carcinoma. These carcinomas, on the other hand, lack K5 expression. Chordomas also consistently express neuron-specific enolase and, focally, synaptophysin, but they never express chromogranin. In contrast, pituitary adenomas that enter in the differential diagnosis of chordomas of the clivus regularly express the full spectrum of neuroendocrine markers and differ from chordoma by having a narrower repertoire of keratins, often lacking expression of K8 and K19. Immunohistochemistry is especially useful in the diagnosis of chordoma in small biopsy specimens that offer limited material for morphologic observation.45

**Adamantinoma** -- Adamantinoma of long bones is a rare skeletal tumor of unknown origin with epithelial and fibrous elements. The ill-defined distinction between the two components led to the assumption that these tumors might be derived from a mesenchymal stem cell. It has been shown that collagens I and III and fibronectin are expressed only in the osteofibrous component, while the epithelial component is surrounded by a more or less continuous basement membrane. It has been suggested that in adamantinoma, individual epithelial cells transform from the osteofibrous component and form the clusters of epithelium recognized in classic adamantinoma. This is analogous to the origin of the glandular component in biphasic synovial sarcoma. However, the fibrous component in adamantinoma is believed to be of benign nature. These results also support the hypothesis of osteofibrous dysplasia as a potential precursor lesion of adamantinoma.46
Conclusions

Although immunohistochemistry does not currently play the important diagnostic role in primary bone tumors that it plays in soft-tissue counterparts, research efforts to characterize the histogenesis of many of these neoplasias may offer new alternatives for diagnosis in the near future. For the distinction of primary tumors vs metastases of non-osseous origin and for the characterization of a small subset of neoplasias, such as those with small round-cell morphology, immunohistochemistry remains the technique of choice.

References


