Diagnostic Tumor Markers – A Review Article

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Abstract :

Tumor markers are substances that can be found in the body when cancer is present. They are most often found in the blood or urine, but they can also be found in tumors and other tissue. They can be products of the cancer cells themselves, or made by the body in response to cancer or other conditions. Most tumor markers are proteins. Tumor markers are substances that can be detected in higher-than-normal amounts in the blood, urine, or body tissues of some patients with certain types of cancer. A tumor marker may be made by a tumor itself or by the body in response to the tumor. Such a substance serves to "mark" the tumor; it is a "tumor marker".tumor markers are biochemical indicators of the presence of a tumor. They include cell-surface antigens,cytoplasmic proteins, enzymes, and hormones.

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Introduction

Soft-tissue tumors are rare neoplasms. Benign tumors occur with an annual incidence of 300 per 100,000 population and outnumber malignant tumors by a margin of approximately 100:1.[1] Malignant soft-tissue tumors, therefore, constitute less than 1% of all cancers. Due to their rarity as well as the wide variation and frequent overlap in their histopathological features, accurate diagnosis of soft-tissue tumors is a constant challenge to pathologists. For these reasons, close communication among pathologists, radiologists, and surgeons is as essential in the evaluation of soft-tissue tumors as it is in the evaluation of tumors of the bone. In many cases, a diagnosis can be reached with confidence by histopathology alone, but in certain cases, even the application of the full armamentarium of available diagnostic methods leaves the pathologist uncertain about the exact nature of the neoplasm. In many situations, however, treatment may not differ for tumors of similar histological grade, regardless of the cell of origin, and the clinician is usually satisfied knowing the histological grade and the status of the margins of resection.

Over the years, the role of one of these ancillary procedures,Immunohisto chemistry(IHC),has greatly enhanced our capabilities to properly classify certain entities. Interpretation of IHC results, however, is dependent on proper technique, strict use and interpretation of well-characterized positive and negative controls, and detailed knowledge about the performance of reagents.

Pathologists must proceed cautiously and consider IHC results in the context of all available data in a given case. This is due in part to our limited understanding of the ontogenesis of soft-tissue tumors and to the demonstrated tendency to aberrant antigen expression in neoplasias in general and soft-tissue tumors in particular. Therefore, pathologists must be aware not only of the typical profile and reported antigenic infidelities of a particular entity, but also of the pitfalls that can be introduced by technical factors, such as tissue processing and fixation as well as the IHC procedures themselves. It is estimated that IHC is confirmatory of a single diagnosis in 30% to 40% of cases, it is helpful in guiding the differential diagnosis in 50% to 60% of cases, and it is not contributory in 1% to 2% of cases. IHC in fact adds confusion to the diagnostic process in 5% to 10% of cases.[3]

Mesenchymal Marker

Vimentin -- Although of limited value in diagnosis, vimentin, a mesenchymal intermediate filament, can be demonstrated in most properly fixed tissues and therefore is used to identify antigen loss during processing. Thus, if vimentin is not identified in tissue that should express it, the test sample should be interpreted cautiously or entirely avoided.

Neuronal, Nerve Sheath, And Melanocytic Markers

S-100 Protein (S-100) -- Widely distributed in peripheral and central nervous systems, the S-100 protein may play a role in ionic regulation. It localizes to both the nucleus and the cytoplasm and, given the appropriate histology and a specific differential diagnosis, S-100 is one of the most useful markers. It is expressed in astrocytes, oligodendrocytes, Schwann cells, adenohypophysis, adrenal medulla, and a variety of other cells including chondrocytes, adipocytes, histiocytes, and interdigitating reticulum cells of the lymph nodes. Neurofibromas and neurilemmomas express S-100 diffusely, and 50% to 70% of malignant peripheral nerve sheath tumors express S-100 focally. S-100 is also expressed in 90% of clear-cell sarcomas or melanoma of soft parts, occasionally expressed in leiomyomas and leiomyosarcoma, liposacomas, ossifying fibromyxoid tumors, and rarely expressed in synovial sarcomas and chondrosarcomas. Melanomas express S-100, a feature that helps in the differential diagnosis of sarcoma-like melanomas. Chordomas coexpress both S-100 and cytokeratins.[4]

HMB45 -- The antigen recognized by this antibody is located in premelanosomal vesicles. HMB45 is very helpful for melanocytic lesions and related entities since it is expressed in 89% of melanomas, almost all clear-cell sarcomas, and tumors related to tuberous sclerosis (rhabdomyoma, angiomyolipoma, and lymphangiomatosis). However, it is expressed in only 22% of desmoplastic, neurotropic spindle-cell melanomas. HMB45 is not expressed by alveolar soft-part sarcoma, chondroid lipoma, leiomyoma, leiomyosarcoma, malignant peripheral nerve sheath tumors, or ossifying fibromyxoid tumors.[5]

Neurofilament Protein -- Useful in the differential diagnosis of small round-cell tumors, neurofilament protein is expressed by many neuroblastomas, medulloblastomas, retinoblastomas, and peripheral neuroepitheliomas, and it is expressed focally in rhabdomyosarcoma and occasionally in malignant fibrous histiocytoma. It has also been demonstrated in Merkel cell tumors and tumors of endocrine origin.[6]

Leu-7 (CD57) -- An antigenic marker for natural killer cells, Leu-7 can be expressed by a variety of neuroendocrine and non-neuroendocrine tumors. Although expressed in nerve sheath tumors and small round-cell tumors of childhood such as neuroblastoma, prominent expression in rhabdomyosarcoma limits its use in the differential of small round-cell tumors.[7]

Synaptophysin -- Present in the presynaptic vesicles of nerve cells, synaptophysin is expressed by tumors of neuronal origin including neuroblastoma, ganglioneuro-blastoma, olfactory neuroblastoma, melanotic neuroectodermal tumor of infancy, peripheral neuroepitheliomas, and rare rhando-myosarcomas.[8]

Neuron-Specific Enolase -- The use of neuron-specific enolase is limited due to frequent, nonspecific background staining, particularly when polyclonal antibodies are used. It is expressed in over 50% of neuroblastomas, paragangliomas, and various endocrine tumors, in one third of malignant melanomas, and in 2% of nonneural tumors.[9]

Myelin Basic Protein -- This protein constitutes approximately one third of the myelin sheath and can be identified in benign and malignant Schwann cell tumors and granular cell tumors. It may be useful to distinguish malignant schwannoma from malignant melanoma.[10]

Chromogranin -- This protein is a member of a family of acidic glycoproteins (the most abundant is chromogranin A) located in the soluble fraction of neurosecretory granules. It is used as a panendocrine marker since it is expressed by a majority of neuroendocrine tumors.[11]

Endothelial/vascular Markers

CD31 -- The antigen, GPIIa, the cellular adhesion molecule PECAM-1 (platelet

endothelial cell adhesion molecule), belongs to the immunoglobulin superfamily and is expressed by some hematopoietic and endothelial cells. It has been shown to have a sensitivity and specificity of 100% for endothelial lesions. It is expressed by 80% to 100% of angiosarcomas and hemangiomas. However, it is also weakly expressed by rare carcinomas and mesotheliomas and in rheumatoid arthritis.[12]

Factor VIII Antigen (FVIII) -- This is a complex of factor VIII-C (anti-hemophilic factor) and factor VIII-associated antigen (von Willebrand factor). Restricted to endothelial cells and megakaryocytes, it is less specific for endothelial neoplasms than CD31 and CD34. However, it is useful as a confirmatory marker, particularly in well-differentiated tumors.[13]

Blood Group Antigens (ABO) -- Ulex lectin, derived from Ulex europaeus, binds to the H substance of the ABO system. It seems to be more sensitive than factor VIII in the recognition of endothelium and angiosarcomas. However, it is less specific since it also recognizes a variety of normal cells and some sarcomas.[14]

CD34 -- The antigen CD34, a transmembrane glycoprotein present on human progenitor cells and endothelial cells, is a very sensitive marker for endothelial differentiation, staining neoplastic endothelium more strongly than normal endothelium. It is expressed by 70% of angiosarcomas, 90% of Kaposi's sarcomas, and 100% of epithelioid hemangioendotheliomas. However, CD34 has a much broader reactivity. It is expressed by certain cells around skin adnexal structures and by nerve sheath lesions, benign and malignant solitary fibrous tumors, gastrointestinal tumors, and 50% of epithelioid sarcomas.[15] The coexpression of CD34 and cytokeratin is observed in epithelioid sarcomas, epithelioid angiosarcoma, and glandular schwannoma. Also, 88% of dermatofibrosarcoma protuberans expressed CD34 compared with only rare cases of benign fibrous histiocytoma and dermatofibroma. CD34 in conjunction with F13a is used in the differential diagnosis of superficial spindle-cell lesions. Both markers are expressed by Kaposi's sarcoma and are absent in keloids. In dermatofibrosarcoma protuberans, CD34 is expressed while F13a is not. The opposite is true for benign fibrous histiocytoma and dermatofibroma.[16]

Muscle Markers

Desmin (Des) -- This intermediate filament of skeletal (Z zone), cardiac, and smooth muscle (dense bodies) is expressed in 95% of rhabdomyosarcomas (sometimes only focally) and variably by smooth muscle tumors. It is also expressed in myofibroblasts, reticulum cells of lymph nodes, endometrial stromal cells, fetal mesothelium, stromal cells of the kidney, and chorionic villi, and it is expressed in 17% of non-myogenic soft-tissue tumors such as malignant fibrous histiocytoma, some fibromatosis, and rare lung carcinomas.[17]

Actins -- These contractile proteins are classified as alpha (skeletal, cardiac, and smooth muscle), beta (cytoplasmic), and gamma (smooth muscle and cytoplasmic).[18] Muscle-specific actin recognizes all alpha actins (skeletal, smooth, and cardiac) and gamma smooth muscle actin. It does not react with non-muscle actins. The pattern of reactivity is usually at the periphery of the cytoplasm. Fibromatosis, fibrohistiocytic lesions, malignant fibrous histiocytoma, and myoepithelial lesions may express muscle-specific actin. The specificity of smooth muscle actin is more restricted than muscle-specific actin. It does not detect skeletal and cardiac (alpha actins) or gamma smooth muscle actins. It is expressed in smooth muscle neoplasms and in non-smooth muscle lesions with myoid differentiation such as nodular fasciitis and myofibroblastic lesions, which are characterized by expression of smooth muscle actin and muscle-specific actin but lack expression of desmin.

Myoglobin -- This marker is expressed only in skeletal muscle and in approximately half of rhabdomyosarcomas. Careful interpretation is required because it can be released from adjacent damaged muscle and phagocytosed by neoplastic and non-neoplastic cells.[19]

Fibrohistiocytic Markers

CD68 -- This 110-kd glycoprotein is found in the lysosomes of monocytes and macrophages and in primary granules of neutrophils found in normal hepatocytes, renal tubules, and melanomas, as well as potentially in any tumor containing lysosomal granules or phagolysosomes. Since it is variably expressed in approximately 50% of malignant fibrous histiocytoma cases, it is considered not specific of this diagnosis. Expression of CD68 should not be used as evidence of histiocytic lineage.[20]

Factor XIIIa (F13a) -- This intracellular form of the fibrin-stabilizing factor is found in serum and may be engulfed by neoplastic cells instead of being actively produced. It is expressed by histiocytic cells such as the dermal dendrocyte, which also expresses CD34. F13a can be used in the differential diagnosis of benign fibrous histiocytoma/dermatofibroma vs dermatofibrosarcoma protuberans (see above) and juvenile xanthogranuloma vs histiocytosis X.[21]

Epithelial Markers

Epithelial Membrane Antigen (EMA) -- This antigen represents a complex of high-molecular-weight cytokeratins isolated from the human milk fat globule (HMFG) membrane. Approximately 75% of the epithelial-like sarcomas (epithelioid and synovial sarcomas) express EMA. EMA is also expressed in perineural tissues, malignant peripheral nerve sheath tumors, leiomyosarcomas, surface of plasma cells, histiocytes, and T-cell lymphomas.[22]

Cytokeratins -- Cytokeratins consist of a group of 19 polypeptides with molecular weights ranging from 40 to 67 K. Cytokeratins are expressed in the vast majority of, if not all, epithelial-like sarcomas such as epithelioid and synovial sarcomas, in many rhabdoid tumors, and in mesotheliomas. Cytokeratins, particularly 8 and 18, are expressed transiently in many mesenchymal cells, a phenomenon more readily apparent in frozen sections and demonstrated at the mRNA level. Whether this represent a regression to the embryonic stage, a result of cell proliferation, or some other reason is unclear. To complicate matters further, many sarcomatoid carcinomas lack diffuse expression of cytokeratins and may aberrantly express other mesenchymal markers.[23]

Conclusions

The availability of high-quality reagents and the improvement, simplification, and automation of procedures have made IHC an indispensable tool for the solution of the diagnostic challenges facing the pathologist. In the field of soft-tissue pathology, IHC, on the one hand, has confirmed the diagnostic accuracy of previous generations of pathologists who, based on morphology alone, have made sense of a frightening number of entities. On the other hand, it has revealed the inherent capabilities of histogenetically unrelated tumors to adopt variable and often overlapping morphological features. Today, the role of IHC is so firmly established that pathologists often tend to rely on its results in detriment of careful histopathological analysis. The increase in the number of applications and the use of an unnecessarily large number of markers may lead to unnecessary costs. These can be reduced by gaining a good knowledge of the sensitivity, specificity, and potential pitfalls of reagents and by optimizing the application and proper interpretation of results. In general, it is advisable to use a limited number of markers as a first step and then expand the number of tests accordingly

References

1. Rydholm A, Berg NO, Gullberg B, et al 1984. Epidemiology of soft-tissue sarcoma in the locomotor system. A retrospective population-based study of the inter-relationships between clinical and morphologic variables. Acta Pathol Microbiol Immunol Scand.92:363-374.
2. Kempson RL, Hendrickson MR 1996. An approach to the diagnosis of soft tissue tumors. Monogr Pathol. 38:1-36.
3. Brooks JS. 1996. Immunohistochemistry in the differential diagnosis of soft tissue tumors. Monogr Pathol. 38:65-128.
4. Nakajima T, Kameya T, Watanabe S, et al 1984. S100 protein distribution in normal and neoplastic tissues. In: DeLellis R, ed. Advances in Immunohistochemistry. New York, NY: Mason 141-158.
5. Bacchi CE, Gown AM 1992. Specificity of antibody HMB-45. Arch Pathol Lab Med.116:899-900.
6. Roessmann U, Velasco ME, Gambetti P, et al. 1983. Neuronal and astrocytic differentiation in human neuroepithelial neoplasms. An immunohistochemical study. J Neuropathol Exp Neurol.42:113-121.
7. Arber DA, Weiss LM. 1995. CD57: a review. Appl Immunohistochem.3:137-152.
8. Gould VE, Lee I, Wiedenmann B, et al. 1986. Synaptophysin: a novel marker for neurons, certain neuroendocrine cells, and their neoplasms. Hum Pathol.17:979-983.
9. Lloyd RV, Warner TF. 1984. Immunohistochemistry of neuron specific enolase. In: DeLellis RA, ed. Advances in Immunohistochemistry. New York, NY: Mason:127-134.
10. Itoyama Y, Sternberger NH, Kies MW, et al. 1980. Immunocytochemical method to identify myelin basic protein in oligodendroglia and myelin sheaths of the human nervous system. Ann Neurol.s7:157-166.
11. Lloyd RV, Wilson BS. 1983. Specific endocrine tissue marker defined by a monoclonal antibody. Science.222:628-630.
12. Longacre TA, Rouse RV. 1994. CD31: a new marker for vascular neoplasia. Adv Anat Pathol.;1:16-20.
13. Millard PR, Heryet AR. 1985. An immunohistological study of factor VIII related antigen and Kaposi's sarcoma using polyclonal and monoclonal antibodies. J Pathol.;146: 31-38.
14. Holthofer H, Virtanen I, Kariniemi AL, et al. 1982. Ulex europaeus I lectin as a marker for vascular endothelium in human tissues. Lab Invest.47:60-66.
15. Miettinen M, Lindenmayer AE, Chaubal A. 1994. Endothelial cell markers CD31, CD34, and BNH9 antibody to H- and Y-antigens--evaluation of their specificity and sensitivity in the diagnosis of vascular tumors and comparison with von Willebrand factor. Mod Pathol.;7:82-90.
16. Cohen PR, Rapin RP, Farhood AI. 1994. Dermatofibroma and dermatofibrosarcoma protuberans: differential expression of CD34 and factor XIIIa. Am J Dermatopathol.16:573-574.
17. Truong LD, Rangdaeng S, Cagle P, et al. 1990. The diagnostic utility of desmin. A study of 584 cases and review of the literature. Am J Clin Pathol.93:305-314.
18. Franquemont DW. 1993. Muscle- actin antibodies. Am J Clin Pathol.99:353.
19. Dias P, Parham DM, Shapiro DN, et al. 1992. Monoclonal antibodies to the myogenic regulatory protein MyoD1: epitope mapping and diagnostic utility. Cancer Res. 52:6431-6439.
20. Weiss LM, Arber DA, Chang KL. 1994. CD68: a review. Appl Immunohistochem.2:2-8.
21. Takata M, Imai T, Hirone T. 1990. Factor XIIIa positive cells in normal peripheral nerves and cutaneous neurofibromas of type 1 neurofibromatosis. Am J Dermatol.126: 472-476.
22. Swanson C, Perentes E, Phillips L, et al. 1992. Epithelial membrane antigen reactivity in mesenchymal neoplasms: an immunohistochemical study of 306 soft tissue sarcomas. Surg Pathol.2:313-322.
23. Miettinen M. 1991. Keratin subsets in spindle cell sarcomas. Keratins are widespread but synovial sarcoma contains a distinctive keratin polypeptide pattern and desmoplakins. Am J Pathol.138:505-513.