Review

Diagnostic Immunohistochemistry of Mesenchymal Tumors

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Since immunohistochemical procedures started to be used in the field of tumor pathology, they have been actively applied to the study of soft tissue tumors as techniques which remove much of the difficulty involved in histological diagnosis. A number of reports are available to show that these procedures have successfully yielded objective findings which allow for diagnostic agreement in many cases. Another opinion is that what is most important in the diagnosis of soft tissue tumors is an accurate determination of the morphological characteristics, making it doubtful that immunostaining

would be performed unnecessarily because the accurate determination of morphological characteristics allows for the diagnosis of almost all soft tissue tumors. Clearly, the point that it is important to determine morphological characteristics is quite right. It is also a fact that many soft tissue tumors can be diagnosed without immunostaining. However, there are also a large number of patients for whom definite diagnosis can be made only after immunostaining and in whom reconfirmation by immunostaining is needed before a final diagnosis is made.

Key words: Immunohistochemistry, Soft tissue tumor, Cytoskeleton, HMB-45

I. Introduction

The application of immunohistochemical staining to the diagnosis of soft tissue tumors had already become widely used among surgical pathologists through the 1980s when its application prevailed [3, 5–18]. The technique has become so common among them that it is impossible to diagnose soft tissue tumors without this technique.

Quite a large number of studies have revealed numerous markers that are useful for differential diagnosis of soft tissue tumors. Typical markers are shown in Tables 1 and 2. Almost all surgical pathologists already know these markers, and should have been using them frequently in routine work for diagnosing soft tissue tumors. Therefore, it is not necessary to describe each of these markers in detail.

There are many that hold that what is most important

in the diagnosis of soft tissue tumors is to accurately determine the morphological characteristics, and it is doubtful that immunostaining would be performed unnecessarily because the accurate determination of morphological characteristics allows for the diagnosing of almost all soft tissue tumors. Certainly, such an opinion showing that it is important to determine morphological characteristics is quite right. It is also a fact that many soft tissue tumors can be diagnosed without immunostaining. However, there are a large number of patients for whom definite diagnosis can be made only after immunostaining and in whom reconfirmation by immunostaining is needed before a final diagnosis can be made. Here, I present some patients who could receive final diagnoses only by immunostaining.

II. Case Examples

At first, some patients for whom immunostaining was extremely effective in making a final diagnosis are shown.

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Table 1. *Common antigens in soft tissue tumors*

Tumors	Antigens
Skeletal muscle tumors	myoglobin, CPK-MM, β -enolase, Myo D1
Neural tumors	S-100 protein, Leu 7, synaptophysin, neuron-specific enolase, CD57, nerve growth factor receptor
Vascular tumors	factor VIII-related antigen, UEA-1, CD34, CD31, blood group isoantigen
Adipose tissue tumors	S-100 protein
Cartilaginous tumors	S-100 protein
Tumors with epithelial differentiation	epithelial membrane antigen, carcinoembryonic antigen
Melanocytic tumors	S-100 protein, HMB-45
Ewing's sarcoma, PNET	MIC-2 gene product p30/32

Table 2. *Cytoskeleton in soft tissue tumors*

Antigens	Tumors
Muscle actin (HHF-35)	Skeletal and smooth muscle tumors Various tumors and pseudotumors with myofibroblastic differentiation
α -Smooth muscle actin	Smooth muscle tumors Various tumors and pseudotumors with myofibroblastic differentiation
α -sarcomeric actin	Skeletal muscle tumors
Cytokeratin	Mesothelioma, Synovial sarcoma, Epithelioid sarcoma, Chordoma, Rhabdoid tumor, (Other tumors)
Vimentin	Most soft tissue tumors
Desmin	Skeletal and smooth muscle tumors (Other tumors)
Neurofilament	Neuroblastoma, Ganglioneuroma, Ganglioneuroblastoma, Paraganglioma Malignant peripheral nerve sheath tumor
Glial fibrillary acidic protein	Schannoma, Malignant peripheral nerve sheath tumor

Spindle cell rhabdomyosarcoma

A 15-year-old boy visited our hospital complaining of severe pain in the scrotum. Under the diagnosis of torsion of the testis or a testicular tumor, total orchiectomy was performed. The excised testis showed widespread hemorrhage and necrosis, and there was no viable testicular tissue. The peritesticular tissue also showed widespread necrosis, and the greater part of the remaining viable tissue contained granulation tissue and fibrous connective tissue. From these histological features the diagnosis of widespread necrosis and hemorrhage due to the torsion was considered. However, detailed observation revealed a small number of large spindle cells with eosinophilic cytoplasm. They did not show marked nuclear atypia, but they were large and their morphology was different from that of fibroblasts (Fig. 1A). This

finding also suggested the possibility of spindle cell rhabdomyosarcoma, but no definite diagnosis was made because the quantity of the viable tissue was too small. In immunostaining, the eosinophilic large spindle cells were strongly positive for muscle actin, desmin, and myoglobin (Fig. 1B). Therefore, the tumor could be diagnosed as spindle cell rhabdomyosarcoma.

Metastasis of paraganglioma

Another patient was a 28-year-old man. He visited our hospital with a complaint of pain in the left hip joint. Roentgenographically, the patient was suspected of having a giant cell tumor or an aneurysmal bone cyst of the head of left femur, and received curettage. The tumor part was cystic and markedly hemorrhagic. An aneurysmal bone cyst was most suspected. The histological examina-

Fig. 1. The tumor tissue of the scrotum of a 15 year-old boy. **A:** The tumor consisted of large spindle cells with eosinophilic cytoplasm. They did not show marked nuclear atypia (H-E, $\times 75$). **B:** Immunohistochemically, the many tumor cells were positive for myoglobin ($\times 75$).

tion revealed tumor tissue against a background of marked hemorrhage. Because of hemorrhage and artifacts due to curettage, the collapse of tissue architecture was marked and characteristics of the tumor tissue were not clear, but oval to polygonal tumor cells of moderate size appeared to have shown alveolar proliferation (Fig. 2A). I was convinced that the tumor was metastatic, and performed immunostaining. On this occasion, the possibility of metastasis of a paraganglioma, as well as that of cancer

metastasis, was considered. The tumor cells were strongly positive for chromogranin (Fig. 2B). S-100 protein-positive sustentacular cells were also observed. From these findings, the tumor could be diagnosed as a metastasis of paraganglioma. On the basis of this result, systemic screening was performed, and revealed a paraganglioma in the retroperitoneum.

These two patients described above are good examples of the fact that no correct diagnosis could have

Fig. 2. The tumor tissue of the head of the left femur of a 28-year-old man. **A:** The tumor tissue against a background of marked hemorrhage (arrows) ($\times 30$). **B:** Immunohistochemically, oval to polygonal tumor cells of moderate size are positive for chromogranin ($\times 150$).

been achieved without immunostaining. The following two patients needed confirmation by immunostaining before final diagnoses were made.

Epithelioid hemangioendothelioma

A 51-year-old woman showed multiple nodular shadows in the lungs. With a clinical diagnosis of metastatic lung cancer, a transbronchial lung biopsy was performed. Histologically, nodules with abundant myx-

oid matrices were observed in the alveolar area. A small number of short spindle to oval cells were present against a background of these myxoid matrices (Fig. 3A), but there were many cells with vacuoles among these cells. From the patient's age, 51 years, roentgenographic findings, and the histological features, there was not much doubt that the tumor was an epithelioid hemangioendothelioma, but it had been clinically diagnosed as metastatic lung cancer. These observations suggested the need for confirmation by

Fig. 3. The transbronchial lung biopsy specimen of a 51-year-old woman. **A:** A small number of short spindle to oval cells were present against a background of myxoid matrices ($\times 75$). **B:** Immunohistochemically, these cells were positive for factor VIII-related antigen ($\times 150$).

immunostaining. The tumor cells were positive for factor VIII-related antigen (Fig. 3B), and a definite diagnosis was made.

Intravascular fasciitis

Another patient was a 26-year-old man. He presented with a tumor mass of the right thenar eminence. The mass was excised. Histological examination revealed dense proliferation of spindle cells without atypia and with

slight inflammatory cell infiltration. Furthermore, particularly noteworthy was the fact that proliferating spindle cells were distinctly infiltrating blood vessels (Fig. 4A). From these findings, intravascular fasciitis was considered, but immunostaining was performed, because, if the tumor was intravascular fasciitis, the proliferating spindle cells should show a staining pattern like that of myofibroblasts. The spindle cells were positive for muscle actin, but distinctly showed a weaker pattern of staining than that

Fig. 4. The tumor tissue of the right thenar eminence of a 26-year-old man. **A:** The tumor consisted of spindle cells without atypia. These cells were also infiltrating blood vessels ($\times 30$). **B:** Immunohistochemically, these cells were positive for muscle actin, but distinctly showed a weaker pattern of staining than of smooth muscle cells of blood vessels ($\times 75$).

of smooth muscle cells (Fig. 4B), the tumor was finally diagnosed as intravasucular fasciitis. At present, 8 years after the final diagnosis, the patient has no recurrence or metastasis of the tumor.

Angiomyolipoma with sarcomatoid features

The final example is related to a monoclonal antibody, HMB-45. Recently, it became known that not only malignant melanoma and clear cell sarcoma but also

angiomyolipoma of the kidney and the liver as well as pulmonary lymphangiomyomatosis are positive with the antibody [1, 2, 4]. It is well known that angiomyolipoma often shows histological features by which angiomyolipoma is confused with a malignant tumor. There is even a case that shows these sarcomatoid features alone (Fig. 5A). In such a case, differentiation of angiomyolipoma from renal cell carcinoma and sarcoma may become an issue. It has also become well known that

Fig. 5. A: Angiomyolipoma of the kidney with sarcomatoid features alone ($\times 30$). B: Immunohistochemically, the atypical large tumor cells were positive for HMB-45 ($\times 150$).

immunostaining using HMB-45 is extremely effective for such a case (Fig. 5B).

III. Conclusions

As presented above, there are many patients with soft tissue tumors for whom immunostaining was very useful for correct diagnoses. Although it is no exaggeration to say that the immunohistochemistry of soft tissue tumors has undergone explosive development, it is expected that

further details of various specific proteins will be clarified, resulting in an extension of the range of their application.

IV. References

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