

# Immunohistochemistry Particularities of Retroperitoneal Tumors

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*Retroperitoneal space is called sometimes no man's land" and for a good reason: this is disputed anatomical territory for many surgical and medical specialties. Their wide histological diversity and unspecific clinical presentation make them a challenge for the surgeon. In order to improve their detection immunohistochemistry seems to show promising results. Methods of detection have evolved over time to identify as much as possible the histological type of tumor. Because of this extreme variability immunohistochemistry through its various markers is the one that often sets the definitive diagnosis, the simple histopathological examination being insufficient. This paper aims to highlight the main markers used in retroperitoneal tumors. As it can be seen there is a huge histologic areal for these tumors. Some have proven some of them still not. Given the fact that there is a tendency toward personalized therapy it is imperative to identify the histological type of tumor as soon as possible.*

**Keywords:** immunohistochemistry, tumors, retroperitoneal, marker

Retroperitoneal tumors are a distinct pathology, representing rare conditions associating a histological diversity. Therefore, this disease is often difficult to be precise diagnosed, especially in patients with concomitant pathologies (e.g. diabetes mellitus, chronic kidney disease, malnutrition, other neoplasia etc.) [1-6]. In addition, the treatment, which is so problematic due to lack of guidelines, is very difficult to drive as long as there is no precise histopathological diagnosis. Furthermore, over the years, the classifications have changed (the notion of malignant fibrous histiocytoma has been replaced by pleomorphic sarcoma). All these patients also are in need for specific preoperative management [7,8].

Primary retroperitoneal tumors are mesenchymal tumors with diverse origin points, such as muscles, adipose, connective or vascular tissue, bone, cartilage, deep skin tissue and even from neural tissue (not from retroperitoneal organs) [9,10].

Several studies identified different markers specific for each histological type, but additional time and testing are required to prove their value.

## Experimental part

### Material and method

A thorough research using the words *immunohistochemistry*, *retroperitoneal* and *neoplasia* using PubMed database was conducted.

## Results and discussions

The main types of primitive retroperitoneal tumors are presented in Table 1 along with the most commonly used and accepted immunohistochemical markers. The markers in the study or the particularities of each tumor type are presented gradually to each tumor type in part.

Liposarcoma (LS) is one of the most frequent retroperitoneal (RP) soft tissue sarcoma, with an incidence rate estimated at approximately 45-50%, and 25% of cases it is localized in the extremities [11,12].

According to the 2013 World Health Organization classification of fat tissue tumors, LS can be classified as well differentiated, dedifferentiate, myxoid (including round cell LS) and pleomorphic LS; well differentiated LS (WDLS) and dedifferentiated LS (DDLs) represent the most frequent LS subtypes [13], characterized by the amplification of the chromosome 12q13-15 (the main location for the following proto-oncogenes MDM2, CDK4, HMGA2, TSPAN 31 or SAS). The MDM2 and CDK-4 oncogenes present over a 90% amplification rate, being involved in the initiation of the fat tumor development and detected by molecular techniques (immunohistochemistry). MDM2 amplification is absent in ordinary lipomas, and therefore it represent a valuable tool for the differential diagnosis of LS from lipomas [14].

In the past, malignant fibrous histiocytoma (MFH) was considered a rare sarcoma that originates from histiocytes

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Tumor type	Tissue of origin	Markers
Angiosarcoma	Endothelium	CD31, CD34, FLI-1
Leiomyosarcoma	Smooth muscle	Actin, desmin, heavy myosin chains
Rhabdomyosarcoma	Skeletal muscle	MyoD1, myogenin, actin, desmin
Synovial sarcoma	Unknown	Cytokeratin, EMA
Epithelioid sarcoma	Unknown	Cytokeratin, CD34, INI 1
Malignant Schwannoma	Nervous sheath	S-100, CD57, NGF receptor, EMA, claudina-1, Glut-1
Liposarcoma	Adipocytes	S-100, MDM2, CDK4
Chondrosarcoma	Chondrocytes	S-100
GIST and E-GIST	Cajal cells	CD117a (c-kit), CD34, protein kinase C $\theta$
Hemangiopericytoma	Unknown	CD34, bcl-2
Histiocytoma	Unknown	Desmin, EMA, CD68
Alveolar sarcoma	Unknown	TFE3
Perivascular epithelial tumors PEComa	Unknown	Actin, melanocytic markers
Histiocytic sarcoma	Bone marrow	CD68, CD163, CD4, CD45RO, S-100
Chordomas	Bone	Cytokine
Merkell cell carcinoma	Unknown	CD56, synaptophysin, CKAE/AE3, cytokeratin (CK) 20
Primary extragonadal germ cells	Germ cells	AFP, CK AE1/AE3, Glypican-3, SALL4, PLAP, EMA, CD 117

Table 1  
PRIMITIVE  
RETROPERITONEAL  
TUMORS

and fibroblasts, but, recently, the data showed that retroperitoneal location is the second most frequent location of MFH (approximately 15% of all MFH locations), after the extremities (in 45-50% cases) [15-17]. There are 5 subtypes of MFH: myxoid, storiform-pleomorphic, giant cell, angiomatoid and inflammatory MFH. Several articles have reported that the inflammatory MFH type has the lowest incidence rate while the pleomorphic type has the highest incidence [18,19].

Over the last decade interesting results have been published regarding MFH physiopathology. It has been stated that CD34, CD68 and vimentin (using immunohistochemistry techniques) are important markers in confirming the MFH diagnosis [20-22].

There is also a very rare subtype of histiocytoma - the angiomatoid fibrous histiocytoma (topography includes retroperitoneum, too). Epithelial membrane antigen, desmin, smooth-muscle actin, CD68 and CD99 are usually present in this tumor [23].

Leiomyosarcoma are the second most frequent retroperitoneal neoplasms and therefore many attempts were made to identify the specific markers linked to tumor prognosis. A large study based on 71 cases showed that CREPT (cell-cycle related and expression-elevated protein in tumor, also named RPR1B), Ki 67 and PCNA seem to correlate with tumor prognosis and patients' survival. A total of 56 patients (78.9%) displayed positive CREPT expression, Ki-67 in 49 cases (69.0%), and PCNA expression in 63 cases (88.7%), respectively. There was a significant association between the expression of CREPT and the mitotic count and the histological grade [24].

Soft tissue sarcomas constitute 0.7% of adult malignancies, and 10-20% occur in the retroperitoneum; LMS, liposarcoma and fibrosarcoma are the most common histological types [25].

The novel marker PRUNE2- prune homolog 2, *Drosophila* (a susceptibility gene for Alzheimer disease and an important regulator of Rho signaling) was considered as a valuable tool to differentiate leiomyosarcoma from GIST. It seems that PRUNE2 is an independent favorable prognostic factor for overall survival [26-28].

One of the rarest and aggressive sarcomas is the histiocytic type; it occurs in lymph nodes, skin, and the gastrointestinal tract. Retroperitoneal location is one of its favorites and usually presents with intense positivity for CD68, CD163, CD4, and CD45RO., but also immunoreactivity for S-100 [29]. The differential diagnosis is made with others lymphoproliferative pathologies (i.e. Castleman's disease) [30].

GIST and EGIST-gastro intestinal stromal tumors and extra GIST have basically the same histological origin but different location, prognosis and therapy management [31]. EGIST is a relatively recently discovered group of tumors with approximately 70 cases reported in the literature. We grouped them because of their common histological origin [32, 33].

The gold standard diagnostic test for GIST is through IHC, highlighting c-kit (CD117) - a tyrosine kinase growth factor receptor noticed in majority of these types of lesion [34-38].

In unresectable or metastatic GIST or E-GIST, there is a high probability of resistance occurrence after biologic treatment. In addition, there are rare cases of retroperitoneal GIST that developed rhabdomyosarcomatous (with IHC reactivity at desmin and myogenin) and chondrosarcomatous differentiations (with IHC reactivity at S-100) after the biologic therapy [17].

Rhabdomyosarcoma (RMS) is the most common soft tissue tumor manifesting features of skeletal muscle differentiation, usually occurring in childhood or

adolescence (rarely in adults and the lesions were commonly observed on the head and neck) [39].

Only two cases of retroperitoneal cases have been previously described [40]. These lesions in adults appear to have distinct clinico-pathologic features and a more aggressive clinical course when compared with cases occurring in the pediatric patients [41,42]. There is also one case of woman with spindle cell rhabdomyosarcoma. The case is even more interesting because the tumor symptoms were masked by the pregnancy. Immunohistochemistry revealed strong positive reactions for actin, desmin, myoglobin, myogenin, myoD1, CD99, p53, and Ki 67 [43].

Chordomas are very rare malignant tumors that usually involve the skull base or the axial skeleton (rarely in the retroperitoneum area). If the primary lesion is not well controlled, it will be even more harder to control the relapses or recurrences – especially if the disease relapse appears very late (5 or ten years recurrence interval). Luckily, this type of tumor usually spreads by direct contact rather than lymphatic drainage. Immunohistochemistry for brachyury, cytokeratin should be reviewed and confirmed by an expert pathologist [44].

There are rare reports of isolated cases of primary mucinous neoplasms of the retroperitoneum; there are described mucinous adenocarcinoma with immunohistochemistry involving CA19-9, but not CEA or any ovarian type stroma [45].

There are also many reports of primary mucinous retroperitoneal tumors with uncertain origin; some of them seem to originate from testicular teratomatous or ovarian mucinous tumors, and primary retroperitoneal mucinous cystic neoplasms, or primary pancreatic tumor [46-51]. Even immunohistochemistry presents confounding results regarding the exact origin [52,53].

A very rare type of neoplasia arising in the retroperitoneal space is Merkel cell carcinoma that is usually a skin related cancer (there are cases that appeared primarily in the retroperitoneal space). Immunohistochemistry was positive for CD56, synaptophysin, CKAE/AE3, cytokeratin (CK) 20 staining. On the other hand, the tumors were negative for CD 138, CD 45, CD 99, HMB-45, desmin, myeloperoxidase, S-100, and vimentin [54].

Primary extragonadal germ cells neoplasia represents 1-5% of all germ cells tumors and retroperitoneal site accounts for 4% of all extragonadal germ cell tumors. Yolk sac tumors are the most common and immunohistochemically are positive for AFP, CK AE1/AE3, Glypican-3, SALL4 and negative for EMA and CK7 [55]. Extragonadal seminoma is another type of neoplasia that appears in the retroperitoneal space and usually placental alkaline phosphatase (PLAP) appears positive at immunohistochemistry [56].

On a series of 48 patients with extragonadal cell tumors Yuping Gao et al. found 5 cases with retroperitoneal location: two malignant teratoma, 2 seminoma and 2 yolk sac tumors. After IHC were performed the following were noticed: PLAP and EMA positive in Yolk sac tumor, teratoma stained positive for CK AE1/3 and EMA, and seminoma for PLAP, CD 117 and sometimes for EMA and CK AE1/3 [57,58].

In the literature was described a very rare condition: PHAT – pelvic retroperitoneal pleomorphic hyalinizing angiectatic tumor. Zhi-gang Chu et al. described the case of a 26 years old women with a retroperitoneal pelvic tumor accidentally discovered and the histopathological result confirmed the presence of retroperitoneal PHAT. Immunohistochemistry revealed intense positivity for

vimentin, cluster of differentiation (CD) CD34, CD99, CD117 (focal), and B-cell lymphoma 2 (BCL-2) [59-61].

## Conclusions

Immunohistochemical markers like actin, desmin, S-100 protein, bcl-2 have their established role in diagnosis. Unfortunately, there are many rare retroperitoneal neoplasms who still are difficult to differentiate and need proven markers. There is much effort in this line of research and many markers are still in trial. This article cannot and does not comprise all the histological types of primitive retroperitoneal tumors. It only affords to bring up the most common with emphasis on some rare particular types.

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