REVIEW ARTICLE

Article received on September 30, 2018 and accepted for publishing on February 1, 2019.

Primary retroperitoneal tumors – A brief classification and differential diagnosis

Alexandru Cherciu[1], Lucian Iorga[1], Radu Anghel[1], Dragos Marcu[1,2], Raluca S. Costache[1,2], Ioana Bratu[1], Maria Manea[1]

Abstract: *According to literature the primary retroperitoneal malignant pathology is rare, representing less than 0.5% of all malignancies. In spite of its low incidence, this pathology often proves challenging in terms of diagnosis and treatment. The most com¬mon retroperitoneal malignancy is represented by lymphoma that accounts for approximately 33 % of the retroperitoneal malignancies. Other frequent retroperitoneal tumors are sarcomas: liposarcomas, leiomyosarcomas and malignant fibrous histiocytoma (in order of incidence). We have analyzed the existing data regarding the most common primary retroperitoneal tumors in order to realize a brief classification and their differential diagnosis considering their clinical, imagistic, histopathological and molecular characteristics.*
The technological developments that have been made over the years in terms of imaging investigations, as well as in biomelecular and cytogenetic studies have offered new possibilities for of assessing a retroperitoneal mass in order achieve more precise informations that can guide physicians to better distinguish between different types of retroperitoneal tumors and therefore their therapeutical protocol.

Keywords: *retroperitoneal tumors, diagnosis, imaging investigations*

INTRODUCTION

According to literature, approximately 70% – 80% of the primary retroperitoneal neoplasms it is estimated that are malignant, these tumors accounting for 0.1%–0.2% of all malignancies [1, 2]. These retroperitoneal masses can be divided into solid and cystic tumoral masses [3-5]. Because the treatment options vary, it is useful to be able to distinguish these masses and to diagnose them clearly in order to choose the correct therapeutical protocol. Imaging investigations and biopsy play a crucial role in establishing the tumors characteristics in terms of tumour content, size, shape, wall thickness, the presence of intratumoral septa, calcification, fat, necrosis, detecting the extension of the disease in nearby structures and also distant metastases, as well as in predicting the patients prognosis [1, 6, 7].

Corresponding author: Dragos Marcu
marcuradudragos@yahoo.com

SOLID RETROPERITONEAL TUMORS

Solid retroperitoneal neoplasms can be split into four groups: 1. mesodermal neo-

[1] Dr. Carol Davila University Emergency Central Military Hospital, Bucharest, Romania

[2] Carol Davila University of Medicine and Pharmacy, Faculty of General Medicine, Bucharest, Romania

plasms; 2. neurogenic tumors; 3. germ cell, sex cord, and stromal tumors; 4. lymphoid and hematologic neoplasms [8].

Mesodermal Neoplasms

Retroperitoneal neoplasms are predominantly of mesodermal origin, the most frequent tumors located in the retroperitoneum being liposarcomas, leiomyo-sarcomas and malignant fibrous histiocytoma.

Retroperitoneal sarcomas represent approximately 0.2% of all malignancies, being more frequently discovered during the 6th decade of life. Quite often these retroperitoneal masses are found incidentally during imaging investigations, especially in early disease stages when the patient has no alarming sings, nor symptoms that could alert the patient and raise a question mark. Otherwise, a great percentage of retroperitoneal tumors are detected in advanced stages, when the tumor has important dimensions, often being associated with symptoms related to the nearby organ compression or invasion and therefore being less possible to achieve a complete and oncological surgical resection. The rate of relapse in such cases is high, often these patients will develop distant metastases, more frequently in the lungs, liver, bones and brain [1, 2].

Liposarcoma

Liposarcoma is the most common soft tissue sarcoma encountered in adult patients.This fatty cell tumor usually develops in middle-aged individuals as a mass of submucosal tissue that grows easily without pain and ulceration, yet some lesions can grow rapidly and become ulcerated. The most recent classification of sarcomas identifies five categories of liposarcomas: well differentiated, with adipocytic, sclerosing, and inflammatory subtype, dedifferentiated, myxoid, round cell, pleomorphic.

The histological type appears to be closely related to the anatomical distribution, so the well-differentiated liposarcoma appears more frequently in the soft tissues of both limbs and retroperitoneum, whereas the mixoid/round-cell liposarcomas and the pleomorphic liposarcomas have a striking predilection for limbs.

The tumor usually grows slowly over time, leading to progressive and diffuse abdominal distention and to other symptoms that appear to be secondary to the adjacent organ compression. Physical examination can prove itself to be inconclusive (especially in early stages when the tumor is small and without secondary signs nor symptoms), but in advanced stages (when the tumor has important dimensions) it may prove to be a useful tool in terms of raising the suspicion of a retroperitoneal mass.

Laboratory studies have demonstrated that cytogenetics have an important role in diagnosing lipomatous tumors based on the differences of chromosomal abnormalities between tumor types. The lipoblastoma usually exhibits modifications of bands 8q11-13 and the gene PLAG1 has been involved as the target of chromosomal changes [9].

Another important method used for evaluating these types of tumors is represented by imaging investigations. For example, computer tomography (CT) scanning has proven to be superior to magnetic resonance imaging (MRI) when we are investigating a bone erosion and demineralization, whereas MRI provides information's about the limbs characteristics, describing the fatty nature of the tumor. Liposarcomas usually have well-defined and mostly lobulated margins. The well-differentiated liposarcomas are formed of mainly fat tissue with septa or nodules. Myxoid liposarcomas are described as having a pseudocapsule with a homogeneous or heterogenous aspect. Pleomorphic tumors have a markedly heterogeneous structure. Another imagistic technique that can be used for the diagnosis process is angiography. This invesigation can demonstrate tumor malignancy on the basis of a prominent vascular component, therefore having an important value in planning the therapeutical protocol. The diagnostic procedure for liposarcoma is biopsy. For large (>3 cm) and deep tumors, the diagnosis implies open incisional biopsy accompanied by definitive resection. Fine-needle aspiration (FNA) should be followed by immunohistochemical and histological examination [10, 11].

Immunohistochemical examination is used for excluding other types of sarcoma. Lipid staining may

be helpful, although oil red O stains or Sudan black are insufficient for diagnosis. Helpful stains include the following [12]:

• S-100 – Positive results in fat cells and lipoblasts;

• Alpha-1-antitrypsin – Positive results in malignant fibrous histiocytomas;

• Desmin – Positive results in leiomyosarcomas;

• Myoglobin – Positive results in rhabdomyosarcomas;

• Adipophilin stain to document lipid content in the cytoplasm of the neoplastic cells using formalin-fixed paraffin-embedded issue.

Histologically the identification of lipoblasts is decisive for the diagnosis of liposarcoma. A lipoblast is capable to produce and accumulate non–membrane-bound lipid within its cytoplasm. The most important morphologic features in diagnosing the liposarcoma are the demarcated cytoplasmic lipid that shifts the indentations in an irregular hyperchromatic nucleus and the characteristic scalloping of the nuclear membrane.

Well-differentiated liposarcomas usually contain a predominance of mature fat cells with relatively few, widely scattered lipoblasts. In the sclerosing subtype of a well-differentiated liposarcoma, collagen fibrils that encircle fat cells and lipoblasts make up a prominent part of the matrix.

Myxoid liposarcoma, the most common type, is diagnosed by the observation of a delicate plexiform capillary network that is associated with both primitive mesenchyme-like cells and a variable number of lipoblasts. In the round-cell type, lipoblasts are interspersed among sheets of poorly differentiated round cells.

Poorly differentiated pleomorphic liposarcoma is recognized by a mixture of bizarre, often multivacuolated lipoblasts and atypical stromal cells, many of which contain highly abnormal mitotic figures. Hemorrhagic and necrotic areas are common. Lipoblasts are present [12].

Leyomiosarcoma

Leiomyosarcoma derives from smooth muscle tissue, Wolffian duct remnants or blood vessels, being the second most frequently primary retroperitoneal tumor. This type of sarcoma can grow and reachenormous sizes (>10 cm), being more frequently encountered in female patients, usually in the 5th or 6th decade of life. Histopathologically, it is characterized by large areas of cystic degeneration and necrosis, but calcification is uncommon. Immunohistochemistry (IHC) experimental tests have showed that the tumor cells were significantly stained by desmin and actin antibodies, with some variation in staining intensity in different tumor cells. Relatively frail vimentin staining has been observed, especially if it is compared with the intense vimentin - specific decoration of endothelial cells and fibroblasts. Leiomyosarcoma can manifest itself predominantly as extravascular (62%), intravascular (5%) in the retroperitoneum or it can have a combination of extra- and intravascular components (33%). At CT examination, small tumors are usually homogeneously solid, although large tumors have areas of necrosis and occasional hemorrhage.

Extremely rare, leiomyosarcoma can appear as a cystic tumor. The MRI highlights these tumors to have intermediate to low signal intensity on T1-weighted images and intermediate to high signal intensity on T2-weighted images, depending on the amount of necrosis. So in conclusion, the existence of necrosis in a retroperitoneal tumor, with contiguous involvement of a vessel, is suggestive for leiomyosarcoma. Distant metastases usually occur late in the course of the disease, the most common locations being the liver, the lungs and/or lymph nodes [1, 13].

Approximately 6% of these retroperitoneal tumors arise from the inferior vena cava (IVC) [1]. These tumors have a large extravascular component that makes it difficult to distinguish them from a secondary involvement of the IVC. The most commonly affected location is the segment between the diaphragm and the renal veins. Tumors involving the superior segment of the IVC (above the hepatic veins) may manifest with Budd-Chiari syndrome, those of the middle segment (between the hepatic and renal veins) manifest with right upper quadrant pain, discomfort, nephrotic syndrome, or arterial hypertension [14-17]

and the tumors of the inferior segment of the IVC (below the renal veins) can manifest with pain and lower extremity edema [13]. The differential diagnosis includes benign thrombus, angiosarcoma and a tumor extending to the IVC from adjacent organs [13, 18]. Tumors that develop from the middle segment of the IVC seem to have a better prognosis than those that arise from other IVC segments [18].

Malignant Fibrous Histiocytoma

This type of tumor is the third most common retroperitoneal sarcoma, but overall is the most frequently sarcoma in the body [19]. Malignant histiocytoma derives from primitive mesenchymal elements and it is estimated that approximately 15% of these tumors appear in the retroperitoneum [1]. In terms of gender distribution is it reported that male patients have higher risks for developing this type of tumor (75% male patients versus 25% female patients), being discovered especially in the fifth decade of life. Imaging techniques are nonspecific and usually describe a large, intrusive and heterogeneously enhancing mass with large areas of necrosis and hemorrhage, with invasion of the nearby organs, like other pathologies look alike [20]. Different patterns of calcification can be seen in the peripheral areas of these tumors. A cystic variant with peripheral calcification has been reported. The presence of calcification may help to distinguish leiomyosarcoma from malignant fibrous histiocytoma [1].

Germ cell, sex cord, and stromal cell tumors

Primary extragonadal Germ Cell Tumors

Even though germ cell tumors are present commonly in the testes or ovaries, a slight percent of germ cell tumors arise from an extragonadal location. These tumors are supposed to appear from abnormal primordial germ cell remnants that are cause of: germ cells distributed physiologically to liver, bone marrow, and brain or faulty migration of germ cells from the yolk sac or endoderm to the urogenital ridge [21]. Before an analysis of primary extragonadal germ cell tumor is made, a metastasis should be excluded. Sometimes the primary gonadal tumor could not be detectable because tumor relapse has left only a scar, with asynchronous or synchronous metastasis. This type of tumors is more frequently found in men. From the histopathological point of view, these tumors are classified in nonseminomatous germ cell tumors or seminomas, which involve teratoma, yolk sac tumor, choriocarcinoma, mixed germ cell tumors, and embryonal carcinoma. Increased levels of the beta subunit of human chorionic gonadotropin (choriocarcinoma) and of alpha-fetoprotein (yolk sac tumors, embryonal carcinoma) may be found with laboratory tests [21].

Extragonadal germ cell tumors are frequently seen near the midline, especially between the T6 and S2 vertebrae, the retroperitoneum being the second most common site after the mediastinum, a midline mass being more evocative for a primary extragonadal germ cell tumor than of metastasis. At imaging, the data collected are nonspecific for primary extragonadal germ cell tumors. The imaging characteristics are similar to those of gonadal germ cell tumors. Seminoma is occasionally located in the retroperitoneum and it can be recognized as a lobulated, large, well-defined homogeneous solid mass with fibrous septa and ring-like or speckled calcification. Non-seminomatous germ cell tumors are illustrated as heterogeneous tumors with areas of necrosis, hemorrhage and heterogeneous enhancement. The tumors in the extragonadal sites have a worse prognosis than that of their gonadal counterparts [22].

Lymphoid and Hematologic Neoplasms

The most common retroperitoneal malignancy is represented by lymphoma that accounts for approximately 33% of the retroperitoneal malignancies [1].

Lymphoma can be generally categorized into non-Hodgkin lymphoma and Hodgkin lymphoma. Hodgkin lymphoma usually occurs in patients during their second and sixth decade of life, having a bimodal age of distribution, often involving the spleen and mediastinum, manifesting itself with limited disease. Non-Hodgkin lymphoma is manifested in the forth-seventh decade of life, often associating extranodal disease in the spleen, bowel or liver. It is estimated that paraaortic lymph nodes are affected in 55% of the

patients with non-Hodgkin lymphoma, as well as in 25% of the patients with Hodgkin lymphoma. A retroperitoneal mass can be discovered in approximately 15% of the subjects with non-Hodgkin lymphoma. Mesenteric lymph nodes are also frequently involved in non-Hodgkin lymphoma [1, 2].

At CT, lymphoma is identified as a circumscribed homogeneous mass, with moderate homogeneous contrast enhancement, that disseminates between normal structures without compressing them. The IVC and aorta can be anteriorly modified, producing the imagistic sign called "floating aorta". Necrosis and calcifications are exceptional before therapy [23]. According to literature approximately 23% of the non-Hodgkin lymphomas are heterogeneous and they cannot be differentiated from other primary retroperitoneal tumors on the basis of their enhancement characteristics alone.

Ureterohydronephrosis, with secondary urinary tract infections [24, 25] and IVC obstruction may be found [1].

Image-guided needle biopsy is a first-line investigation when facing such cases, being useful in the diagnosis of lymphoma present in the retroperitoneum, especially if we consider its simplicity, as well as its noninvasiveness, often sparing the patients from radical procedures. Lymphoma comprises a heterogeneous group of lymphoproliferative malignancies, with varying morphologic features depending on the specific subtype [26, 27]. The abnormal lymphocytes in the lymph node, bone marrow, or in extranodal sites can be small, cleaved or noncleaved, intermediate or large cells and they can have a follicular or diffuse pattern. In contrast to reactive follicular hyperplasia, lymphomas usually alter the lymph nodes architecture, the capsule being usually involved [26, 28].

However, needle biopsy encounters several limitations; in few cases, core needle biopsy offers an amount of normal tissue or tissue that has lost its normal architecture, making diagnosis impossible [28, 29].

Immunophenotypic analysis aids to determine neoplastic from reactive lymphoid infiltrates, nonlymphoid from lymphoid malignancies, and specific lymphoid neoplasms. Although bcl-2 expression differentiates reactive follicular hyperplasia from follicular lymphoma, bcl-1 expression strongly supports a diagnosis of mantle cell lymphoma. CD30 expression is also important for the identification of anaplastic large cell lymphoma and it can also be found in the majority of Hodgkin lymphomas. Lymphoma is treated with chemotherapy or radiation therapy [30]. Soft-tissue masses can persist after treatment due to fibrosis and cannot be dif¬ferentiated from viable tumors [31].

Cystic Neoplastic Masses

Retroperitoneal cysts are infrequent, these tumors rarely producing symptoms, usually these symptoms being related to the cysts location and size, as well as to their complications. Differential diagnosis should be made between retroperitoneal cysts and omental, mesenteric, splenic and enteric duplication cysts.

Serous Cystadenocarcinoma

Serous cystadenocarcinoma is a rare primary epithelial retroperitoneal tumor that develops through mucinous or serous metaplasia of retroperitoneal coelomic mesothelium, which is located along ovarian descents [32]. Other approach of expansion includes a supernumerary ovary, an enterogenous cyst and a teratoma. Serous cystadenocarcinoma is discovered in women with normal ovaries. Histopathologically, the mass is multicystic and encapsulated, full with serous fluid and extruding papillary nodules. Imaging techniques are nonspecific and display a defined cystic mass with solid intramural nodules. Increase of the wall and solid components may be found. Other important diagnostic characteristics include: an elevated carcinoembryonic antigen level in the serum andglandular epithelial cells at biopsy [32]. This type of neoplasia needs surgical excision with wide margins [33]. Other rarely primary retroperitoneal epithelial neoplasms are mucinous cystadenocarcinoma, borderline mucinous tumor and borderline serous tumor [32].

CONCLUSIONS

Retroperitoneal masses can appear from different

tissues and are a heterogeneous group, including some rare neoplasms.

Histopathology, immunohistochemistry, imaging techniques and other diagnostic exams are valuable in the evaluation of the retroperitoneal masses, particularly in staging as well as in assessing the nearby invasion. Although for now a specific diagnosis may be difficult to determine due to a lack of diagnostic information, the identification of certain characteristic features, along with clinical and demographic information, may help in narrowing the differential diagnosis.

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