2 Characteristics and Clinical Manifestations of Retroperitoneal Tumor

Cheng-Hua Luo and Chengli Miao

1 Introduction

Primary retroperitoneal tumors (PRPTs) are a group of neoplasms that originate from the retroperitoneal space excluding those arising in the major retroperitoneal organs, such as the liver, duodenum, pancreas, spleen, kidney, suprarenal gland, ureters, and bone. Also excluded are metastatic malignancies from distant sites. Theoretically the tumors originating from the above retroperitoneal organs, e.g., duodenum, pancreas, and suprarenal gland, belong within the scope of "retroperitoneal tumors"; however, they are considered "visceral tumors" in academics. Many scholars still use the term "retroperitoneal tumor" instead of PRPTs. For convenience, in this book, PRPTs are hereinafter referred to as "retroperitoneal tumors."

Tumors located in pelvic retroperitoneum (including retroperitoneal, bilateral peritoneum, inferior and anterior of peritoneum) are also categorized within the scope of retroperitoneal tumors due to the fact they share common biological characteristics and therapeutic strategies with retroperitoneal tumors. The exception is tumors arising from the bladder and prostate.

The origin of retroperitoneal tumors is generally from soft tissue which is defined as non-epithelial extra-skeletal tissues exclusive of the reticuloendothelial system, glia, and supporting tissue of various parenchymal organs. Soft tissue is represented by the skeletal (voluntary) muscles, fat, and fibrous tissue, along with the feeding vessels. It also includes the peripheral nervous system because tumors arising from nerves present as soft tissue masses and are similar in both differential diagnosis and therapy. Embryologically, soft tissue is derived principally from mesoderm with contributions from the neuroectoderm.

Soft tissue tumors are a highly heterogeneous group of neoplasms that are classified based on histology; many of them resemble adult tissue. For example, lipomas and liposarcomas are tumors that recapitulate the normal fatty tissue to various degrees, while hemangiomas and angiosarcomas contain cells with characteristics of vascular endothelium. Within the various histopathological categories, soft tissue tumors are usually divided into benign and malignant types.

Benign tumors more closely resemble normal tissue and have a limited capacity for autonomous growth. These tumors exhibit little tendency to invade locally and have a low incidence of local recurrence following complete excision. To the contrary, malignant tumors or sarcoma is locally aggressive and capable of invasive or destructive growth, recurrence, and distant metastases. Radical surgery is required to ensure relatively complete removal of such tumors. However, the term "sarcoma" does not necessarily indicate the likelihood or rapidity of metastasis. Some types of sarcomas, e.g., malignant fibrous histiocytomas,

C.-H. Luo (✉) • C. Miao
Peking University International Hospital, Beijing, China
e-mail: luochenghua@pkuih.edu.cn

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frequently metastasize, whereas others rarely do. For these reasons, it is essential to qualify the term "sarcoma" by describing the degree of differentiation or the histological grade. "Well differentiated" and "poorly differentiated" are qualitative and subjective terms indicating the relative maturity of the tumor with respect to normal adult tissue. Histologic grade is quantitative and measures the degree of differentiation by employing a set of histologic and cytological criteria. It is well accepted that well-differentiated sarcomas are low-grade lesions, whereas poorly differentiated sarcomas are high-grade neoplasms. There are also intermediate or borderline lesions, whose malignant potential is difficult to be determined. Occasionally, benign tumors or non-tumorous lesions are present with malignant histological features but clinically behave like benign diseases; a canonical example would be pseudosarcomas.

2 Pathogenesis of Retroperitoneal Tumors

As with other malignancies, the pathogenesis and etiology of retroperitoneal tumor remain unclear. Recognized risk factors include physical and chemical factors, exposure to ionizing radiation, and genetic/inherited and acquired immunodeficiency. Due to the long latency period after exposure to hazardous factors and the interaction of multiple environmental and genetic factors, it is difficult to determine the exact cause of such tumors. Retroperitoneal sarcoma that arises from of benign tumors is extremely rare. We have treated several rare cases of benign teratoma that underwent malignant transformation. Malignant peripheral nerve sheath tumors mostly arise from benign type I neurofibromas (von Recklinghausen disease).

2.1 Environmental Factors

Environmental carcinogens have been implicated in the pathogenesis of retroperitoneal sarcoma; however, molecular mechanism has not been explored thoroughly (Newhouse and Thompson 1993). Asbestos is one of the most important environmental carcinogens. A person who inhales asbestos may develop mesothelioma afterward. Phenoxy acid herbicides, chlorophenols, and their contaminants, 2, 3, 7, 8- tetrachlorodibenzo-para-dioxin (TCDD) are involved in retroperitoneal sarcomagenesis. A causal effect of vinyl chloride on hepatic angiosarcoma has been established; this agent may also contribute to the development of retroperitoneal sarcomas.

Radiation exposure is associated with sarcomagenesis (Sindelar et al. 1993). Due to limited population who has undergone abdominal radiotherapy, radiation-induced retroperitoneal sarcoma is extremely rare, and the risk is very low compared to therapeutic benefit from radiotherapy. The incidence of radiotherapy-induced sarcoma has been reported between 0.03% and 0.8% in the literature (Argiris et al. 1995). The diagnostic criteria for radiotherapy-induced sarcoma include sarcoma development within the irradiated field of previous radiotherapy, histologic confirmation of the diagnosis, latency of at least 3 years between irradiation and the presence of a sarcoma, and the region bearing a sarcoma being normal prior to irradiation (Sheppard and Libshitz 2001). The most common postradiation sarcoma is malignant fibrous histiocytoma, which accounts for almost 70% of cases, followed by fibrosarcoma, malignant peripheral nerve sheath tumor, and angiosarcoma. Unfortunately, most postradiation sarcomas are high-grade lesions and diagnosed at a relatively late stage than their sporadic counterparts. Thus, the prognosis of these tumors is dismal, with a 5-year survival rate of less than 5%.

2.2 Oncogenic Viruses

Despite evidence that herpes virus 8 (HHV8) is the causative factor of Kaposi sarcoma, the role of oncogenic viruses in the evolution of retroperitoneal sarcomas is still poorly understood. Accumulating evidence supports the involvement of Epstein-Barr virus in the pathogenesis of smooth muscle tumors in patients with immunodeficiency syndrome or following therapeutic immunosuppression in organ transplantation settings (Lujan and Hoang 2003).

2.3 Immunologic Factors

As mentioned above, immunodeficiency and therapeutic immunosuppression plays a role in the development of retroperitoneal soft tissue sarcomas, particularly smooth muscle tumors and Kaposi sarcoma. Additionally, acquired immunodeficiency or loss of regional immune surveillance may also participate in the pathogenesis of the relatively rare angiosarcomas that arise in the setting of chronic lymphedema, either congenital or secondary to radical mastectomy, or infectious diseases (Naresh et al. 2007).

2.4 Genetic Factors

Numerous genetic diseases have been linked to retroperitoneal tumors (Legius et al. 1994). Classic examples are neurofibromatosis type 1 and type 2, which are previously referred to as peripheral and central neurofibromatosis, respectively. The causal gene for neurofibromatosis type 1 and type 2 is located in the pericentromeric region of chromosome 17 and chromosome 22, respectively. Some cases of retroperitoneal tumors combined with subcutaneous neurofibromatosis have been diagnosed and treated in our hospital. All of these patients had a family history of neurofibromatosis.

Familial adenomatous polyposis (FAP) and the variant Gardner syndrome are caused by adenomatous polyposis coli (APC) gene mutations, often accompanied by mesenteric fibromatosis. Retroperitoneal sarcoma is a type of tumor associated with hereditary familial cancer syndromes (Scott et al. 1996).

3 Epidemiological Characteristics of Retroperitoneal Tumors

Retroperitoneal tumors account for less than 0.5% of all neoplasms. Retroperitoneal tumors are mostly soft tissue tumors and account for 10–20% of the total soft tissue tumors. Of malignant retroperitoneal tumors, 55% are sarcomas. Primary retroperitoneal tumors can occur at any age, but most occur in the 50–60-year-old group as reported in the literature. However, 15% of retroperitoneal tumors occur in children younger than 10 years old. Men account for 50–67% of retroperitoneal tumors. It has been reported that 82% of primary retroperitoneal tumors are malignant, and 5–18% are benign. Many patients with retroperitoneal tumors are never diagnosed. The population incidence has yet to be reported in China. In the United States, soft tissue sarcomas account for less than 1% of all malignant tumors. Nevertheless, the incidence of such tumors has tended to increase worldwide. It is unclear whether this can be ascribed to a true increase in incidence, an improvement in diagnostic techniques, or more public attention paid to such tumors. Up to now, our team has reported 687 cases of retroperitoneal tumors (in China, 2014). Clinicopathological characteristics of our patient population are male 59%, female 41%, benign 25.2%, borderline 6.4%, and malignant 68.4%. The age of onset ranges between 0.3 and 80 years with the median age of 40 years.

4 Oncobiological Characteristics of Retroperitoneal Tumors

Successful therapy of any tumor should be based on understanding of its oncogenic and biological features. Regardless of histologic subtype, primary retroperitoneal tumors generally share the following four common biological phenotypes.

4.1 Expansive Growth Most of the Time

The most important feature is expansive growth while being rarely invasive. Primary retroperitoneal tumors, either benign or malignant, grow by expansion and seldom infiltrate the surrounding tissues or organs, which distinguishes them from other cancers. This unique feature of tumor growth usually causes compression or displacement of adjacent tissue or organs. There are often no symptoms until the tumors become quite large. Due to non-invasiveness, intact capsules

can be identified even for large tumors. A pseudocapsule formed by the tumor pushing against surrounding tissues may be completely resected.

4.2 Tumors Generally Have Intact Capsules

The vast majority of retroperitoneal tumors, either benign or malignant, have complete capsules. This structure can be clearly identified from preoperative imaging, allowing surgeons to perform tumor resection. The key step is to localize accurately the tumor capsule during surgery, sharply dissect the tumor along that line, and thus achieve complete dissection of the tumor while simultaneously minimizing bleeding.

4.3 Tumors Seldom Develop Distant Metastases

In most cases, malignant retroperitoneal tumors, even of very long duration and quite a large size, rarely metastasize through the blood vessels to various distant organs and surrounding lymph nodes, instead, it primarily grows locally. Most patients with retroperitoneal tumors die of organ dysfunction (or failure) resulting from local malignant growth rather than from metastases to distant organs. Even in a late stage, these tumors mainly metastasize through blood vessels and very rarely through lymph nodes. This feature provides the principle for thorough surgical resection of retroperitoneal tumors or combined resection of involved organs/tissues without the corresponding lymph nodes dissection.

4.4 Malignant Retroperitoneal Tumors Are Prone to Local Recurrence

According to the literature and our experience, about 60% of retroperitoneal tumors relapse after surgical resection (DeMatteo et al. 2000). Local recurrence at primary sites or local planting is very common. Satellite lesions are prevalent surrounding retroperitoneal sarcomas, serving as the origin of local recurrence. For recurrent tumors, surgical resection should be strongly considered. Another common cause of recurrence is that the surgeon fails to eradicate the residual tumor tissues adjacent to blood vessels and vital organs, often due to lack of experience. Surgeons familiar with biological features of retroperitoneal tumors should seize every opportunity to surgically remove a large retroperitoneal tumor and perform a complete radical resection. For patient with recurrent tumors, multiple resections are still feasible and are highly recommended.

4.5 Criteria for Total Retroperitoneal Fat Lipectomy in the Treatment of Retroperitoneal Liposarcoma

Retroperitoneal liposarcoma is the most common (41%) primary retroperitoneal soft tissue sarcoma (Nagy et al. 2013). It is difficult to diagnose in its early stage as generally patients do not consult the doctor until the mass has grown to a very large size. Thus, retroperitoneal liposarcoma has a low resection rate and a high recurrence rate. The 5-year local recurrence rate was reported to be 40–60%, accounting for death in 75% of cases.

Surgical resection is the primary therapy of retroperitoneal liposarcoma; however, the diverse biological characteristics and complicated anatomical structures of retroperitoneal liposarcoma have contributed to the high recurrence rate, which seriously affects the clinical outcome (long-term survival rate) of these patients and is the reason why surgical resection has become a great challenge.

The experience of surgery for retroperitoneal liposarcoma has mainly been reported in retrospective studies which limits the strength for recommendation in evidence-based medicine. Nevertheless, it is excited to see some relatively widely accepted results. Multivariate analysis has indicated two important prognostic factors influencing the specific survival rate of retroperitoneal

liposarcoma, i.e., tumor pathological subtypes and gross resection margins. The Memorial Sloan-Kettering Cancer Center has reported the 5-year survival rate of low-grade malignant mucinous liposarcoma as approximately 90% for the well-differentiated subtype with ≤5% round cell area, whereas 30–50%, 60%, and 75%, respectively, for high-grade malignancies, i.e., pleomorphic, round cell (>5% round cell area), and dedifferentiated subtypes (Dotan et al. 2006).

Additionally, the scope of resection is an important predictor for recurrence of retroperitoneal liposarcomas. Complete removal of the tumor to achieve R0 resection (absence of residual tumor cells at the margin under microscope) is an ideal result. However, this goal is almost impossible to be achieved in most retroperitoneal liposarcomas. Firstly, at the time of surgery, retroperitoneal liposarcoma is usually very large and adhere to the surrounding organs. Thus, it is extremely difficult to separate the outer margin of tumor from normal tissue to achieve the entire R0 resection. For this reason, it is well accepted that gross complete resection (R1) of retroperitoneal liposarcoma can significantly reduce its recurrence, which has become a major goal that surgeons in the treatment of retroperitoneal liposarcomas.

In order to achieve gross total resection (R1) of retroperitoneal liposarcomas, some centers strongly recommend regional resection including co-resection of the tumor-infiltrated organs (Strauss 2014). Twenty years ago, many scholars advocated the removal of retroperitoneal liposarcoma combined with the ipsilateral kidney. However, nowadays accumulating evidence has supported that removal of the kidney does not affect the disease-specific survival rate of retroperitoneal liposarcomas. Biological characteristics of renal parapharyngeal sarcomas have shown involvement of renal peritoneal fat capsule in 15%, involvement of renal parenchyma in 9%, and involvement of renal vein in 3% of patients with no involvement of renal tissue in >73% of patients. This observation indicates that retroperitoneal liposarcomas rarely invade renal parenchyma compared with other sarcomas. We now believe that resection of the kidney should be avoided unless the renal hilus circumference is invaded, while the perirenal fat capsule must be removed during surgery for retroperitoneal liposarcomas. Extended surgery, including combined multiple organ resection and perirenal fat capsule excision, namely, regional resection has been widely recognized. European scholars who firstly explored this area have reported that the 5-year recurrence-free and overall survival rate after regional resection of retroperitoneal liposarcoma could approach 55% and 75%, respectively.

Can surgical procedures reduce the recurrence rate of retroperitoneal liposarcoma? This is a vital scientific challenge faced by retroperitoneal tumor surgeons worldwide.

Further investigations have shown that retroperitoneal liposarcoma is often multifocal with satellite foci in normal fat far away from the main tumor body. Many recurrent retroperitoneal liposarcomas are not in situ, but grow at multiple distant sites from the primary location. The retroperitoneal fat invaded by liposarcoma is no longer normal but is "regionally altered (transformed)." It is very difficult to identify these microsatellite lesions in fat tissue during surgery. Based on the above findings, we propose a new surgical procedure for retroperitoneal liposarcoma: total ipsilateral retroperitoneal lipectomy.

The range of total ipsilateral retroperitoneal lipectomy is delineated by the upper border (diaphragm surface), inferior border (iliac vascular surface), lateral border (abdominal wall), medial border (inferior vena cava [to the right] or abdominal aortic [to the left] surface), posterior border (psoas muscle and iliopsoas muscle surface), and anterior border (colon and mesocolon). The contents of surgical excision include the liposarcoma, adipose tissue, perirenal fat capsule, and other organs, which are invaded by the tumor in the above-mentioned range and cannot be separated.

Autopsy findings (unpublished data) have suggested that the ipsilateral retroperitoneal fat is anatomically a contiguous "organ," both from front aspect of view (Fig. 2.1) and from back aspect of view (Fig. 2.2), and it can be treated as an "organ" with no important functions. Total retroperitoneal lipectomy is equivalent to total

Fig. 2.1 Anterior view of autopsy findings in left-sided retroperitoneal fat

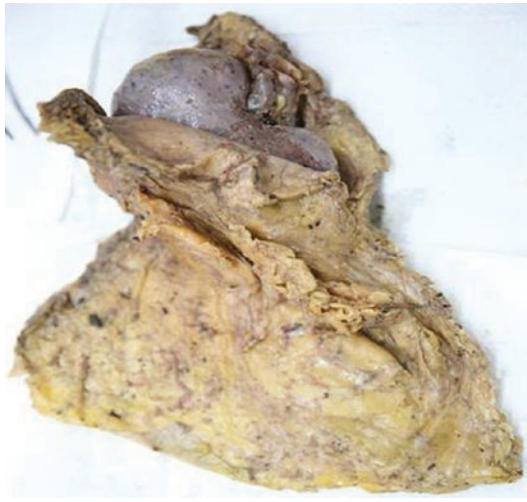

Fig. 2.2 Posterior view of autopsy findings in left-sided retroperitoneal fat

resection of the ipsilateral retroperitoneal fat tissue. It is a safe operation without causing significant physiological or pathological complications. The author is currently conducting a prospective RCT study on total retroperitoneal lipectomy vs. extended regional resection of retroperitoneal liposarcoma in order to assess the clinical value of this procedure.

5 Clinical Presentations of Retroperitoneal Tumor

Retroperitoneal tumor growth in the loose retroperitoneal connective tissue space is limited to the surrounding region (but rarely grows posteriorly and penetrating through the back). Small tumors are usually asymptomatic and can only be possibly detected by physical examination. When the tumor grows much bigger, it causes symptoms as a result of compression and displacement or invasion of adjacent organs. Clinical symptoms of retroperitoneal tumors are determined by specific properties of their primary sites. Tumor compression or infiltration of blood vessels, nerves, or other vital organs or structures can lead to corresponding symptoms and syndromes (Felix et al. 1981).

The most common symptom caused by retroperitoneal tumors is pain, including abdominal pain, low back pain, and leg pain and so on. Abdominal pain or back pain occurs in 44–75% of patients. The nature of pain may be dull, sharp, excruciating, or colicky. Pain mainly localizes at the site of the tumor, however sometimes it is difficult to determine the accurate location of the pain. Direct compression by tumor is the most common cause of abdominal pain, while hydronephrosis as a result of ureteral compression can indirectly induce low back pain. Fortunately, abdominal pain and low back pain usually do not lead to loss of activity.

Gastrointestinal symptoms such as nausea, vomiting, change in bowel habits, and constipation are frequently seen in these patients. Bloating may occur in 4–35% of patients, and some cases even develop intestinal obstruction. Anorexia, weight loss, weakness, and fatigue are observed in 40–50% of patients with advanced-stage retroperitoneal malignant tumors, compared to only 3% of those with early stage disease.

Patients sometimes develop urinary and reproductive symptoms since retroperitoneal tumors are located in the pelvis, adjacent to the kidney or ureters. Urinary tract symptoms such as hematuria, frequent urination, urgent urination, urodynia, and dysuria are common, whereas oliguria

or anuria is rare. These symptoms are caused by urinary tract compression, with or without direct involvement of the kidneys and ureters. Patients with retroperitoneal tumors may develop azotemia (e.g., skin itching) caused by bilateral ureteral obstruction.

Retroperitoneal tumors arising from pelvic peritoneum or spreading to the pelvis may compress or invade sacral or lumbar plexus root, resulting in low back pain that radiates toward unilaterally to both lower extremities. Spinal cord compression caused by tumor infiltration of intervertebral foramen may lead to incontinence and lower limb paralysis. Perineal and lower extremity edema and varicose veins result from obstruction of pelvic veins and lymphatic flux when tumors spread to the pelvis. In this respect, patients present with unilateral and even bilateral lower extremity edema. Tumor-induced acute obstruction of the inferior vena cava leads to lower extremity edema; however, this is not the case in chronic obstruction due to the abundant collateral circulation within the retroperitoneum.

Fever has been reported in 10% of patients with retroperitoneal tumors. It is common in patients with large retroperitoneal liposarcomas, especially in relapsed cases. This may be attributed to dramatic necrosis (or necroptosis) within the tumor, and fever can abate immediately after resection of the tumor. Cancer fever classically is related to retroperitoneal lymphomas.

If retroperitoneal tumors compress the portal or hepatic veins, ascites and abdominal varicose veins may occur; a few cases may experience hematemesis. Occasionally, hypoglycemia may be observed, attributable to insulin-like factors secreted by poorly differentiated retroperitoneal sarcomas, or accelerated utilization of fatty acids pool by large tumors with high rate of metabolism. If tumors infiltrate through the hollow organs within the abdominal cavity, patients may develop acute or chronic gastrointestinal bleeding.

The first visit to clinic for a patient with retroperitoneal tumor usually takes place at 3–6 months after the appearance of symptoms. Sometimes retroperitoneal tumors are detected in patients who receive physical examination only because of abdominal bloating, satiety, and heaviness. About 30% of patients with retroperitoneal tumors initially present with an asymptomatic abdominal mass. As the first presentation of retroperitoneal tumors, such mass is mostly palpated by adult patients themselves or detected by their parents or pediatricians of pediatric patients. Due to lack of specific manifestations, patients with retroperitoneal tumors have generally developed advanced disease when they present with palpable masses, abdominal pain, and gastrointestinal symptoms.

Although the patients' medical history may be suggestive of intra-abdominal diseases, physical examination is the key step in diagnosing retroperitoneal tumors. Abdominal mass can be detected by physical examination in more than 90% of patients vs. only 5% of pelvic masses. Masses with different sizes located in the pelvis may be palpated by digital rectal or vaginal examination, 80% of which result in no tenderness. Retroperitoneal tumors generally do not move with respiratory movements. Tumor movability and hardness are quite important indicators in determining whether the tumor has become fixed to the abdominal wall, pelvic wall, or bone structures. A hard and fixed mass is more suggestive of a malignant nature, teratoma, or hamartoma, etc., while a soft and flexible mass is more indicative of lipoma or liposarcoma. Malignant aggressiveness and resectability of retroperitoneal tumors are not always conferred by the sizes of the lesions.

Metastases of retroperitoneal tumors can cause hepatomegaly, compression, and displacement of the liver. Venous reflux disorders resulting from portal vein obstruction leads to ascites in about 15% of patients with retroperitoneal tumors. Varicose veins of the testicles are clinical manifestations of spermatic vein obstruction, indicating left renal vein obstruction if it occurs on the left side. Hypertension is common in patients with extra-suprarenal paragangliomas. Bleeding tendency is observed in patients with vascular sarcomas.

Other clinical manifestations of retroperitoneal tumors include abdominal and flank tension, abdominal distension, splenomegaly, lymph nodes enlargement, pale face, coughing, shortness of breath, and venous thrombosis, as well as intra-abdominal bleeding, jaundice, cachexia, etc.

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