Retroperitoneal Leiomyosarcoma 15

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1 Introduction

Leiomyosarcoma is a soft tissue sarcoma arising from the uterus, gastrointestinal tract, and soft tissue smooth muscle cells, accounting for 5–10% of all soft tissue sarcomas (Gustafson et al. 1992). It is the third most common soft tissue sarcomas following liposarcoma and malignant fibrous histiocytoma. Nowadays, leiomyosarcoma is generally classified into three categories: (a) leiomyosarcoma in the retroperitoneum or peritoneal cavity, which is the most common type, of which 1/2 to 2/3 occurs in the retroperitoneum (Felix et al. 1981); (b) skin and subcutaneous leiomyosarcoma, with the best prognosis among all the three; and (c) prototype vascular smooth muscle sarcoma, which is the rarest type. Primary retroperitoneal leiomyosarcoma, accounting for 11% of all malignant retroperitoneal tumors, can occur at any age, is mostly seen in people aged 40–70 years, and is more prevalent in women than in men (ratio of 2:1). Most of the tumors grow invasively and are difficult to treat, with dismal prognosis and the lowest survival rate among all soft tissue sarcomas (Mankin et al, 2004).

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2 Etiology

The exact etiology of retroperitoneal leiomyosarcoma remains unknown, which requires further investigation. Several common factors may contribute to the development of leiomyosarcoma including loss of chromosomes 13q14 and q21, EB virus, radiation, and chorionic gonadotropin (β-HCG) (Shvarts et al, 2004).

3 Pathogenesis and Pathobiology

Retroperitoneal leiomyosarcoma may occur anywhere in retroperitoneum and outside of pelvic retroperitoneum, originating from retroperitoneal smooth muscle tissue, such as blood vessels, spermatic cord, embryonic mesonephric duct, and paramesonephric duct remnant, all of which are potential cellular origin of such tumors. Leiomyosarcoma was considered to be malignantly transformed from benign smooth muscle tumor. Nowadays, histologically most of these tumors directly arise from endothelia smooth muscle cells lining small blood vessels. As retroperitoneal leiomyosarcomas are mostly very large in size, clinically it is challenging to determine their actual cellular origin.

Retroperitoneal leiomyosarcoma usually presents gray color and fish-meat-like appearance, with focal hemorrhage, necrosis, or calcifications. The section is gray and wheel shaped, just like

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retroperitoneal leiomyoma. It is easily misdiagnosed as cystic schwannoma when cystic degeneration is obvious. Tumor body is often lobular and wrapped by false capsule composed of tumor cells in the outer layer. Pathological manifestations are as follows: (a) the majority of tumor body is typically composed of pure spindle single cells that are arranged in intersecting fascicles, with centered nucleus, in cigar shape, with little secondary changes (hemorrhage and cystic degeneration); (b) interstitial collagen may be found in some cases in which foamy cells and lymphoid tissue aggregate focally. Tumor cells are characterized by strong eosinophilic, fibrillary, or clear (watery) cytoplasm. Modifications in morphology and structural arrangement are occasionally seen. For example, most or part of the tumor body is composed of epithelial cells, being arranged in diffused sheets or trabecular pattern, or even fence-like pattern that is commonly seen in schwannoma (Paal and Miettinen 2001). Another major feature is the presence of longitudinal filaments within tumor cells. The better the differentiation, the more typical the longitudinal filaments; the poorer the differentiation, the more easily lost the characteristics, leading to disordered cell arrangement.

Morphological character is the most important basis for the diagnosis of leiomyosarcoma, which can be assisted by immunohistochemical staining and electron microscope examination. Well-differentiated smooth muscle cells exhibit Masson trichrome (+) (myofiber) and PAS (+) (glycogen in cytoplasm). Reticular fiber staining shows interfibrillar fine mesh structure. The cells are positive for vimentin and actin. Seventy percent of patients are desmin (+), mostly multifocal, but desmin is negative in high-grade tumors. The cells are generally positive for pan-muscle action (HHF-35). Thirty to forty percent of patients are positive for cytokeratin and S100. Under the electron microscope, parallel-arranged actin filaments, adhesion spots, and endocytic vesicle in cytoplasm are displayed, with dense plaques and complete/incomplete basement membrane around the cells. Leiomyosarcoma generally lacks specific cytogenetic manifestation.

Leiomyosarcoma mainly arises from the retroperitoneal vascular smooth muscle tissue. Retroperitoneal leiomyosarcoma exhibits three major growth patterns: (a) completely extravascular (extraluminal) (62%), (b) completely intravascular (intraluminal) (5%), and (c) both extra- and intraluminal (33%). Tumors located in wide retroperitoneal space can grow very large without significant resistance, thus causing displacement or even invasion of the surrounding organs. They can invade the ovary, kidney, pancreas, spine, and other structures besides the inferior vena cava. A majority of retroperitoneal leiomyosarcoma metastasizes through hematogenous dissemination, more frequently than gastrointestinal leiomyosarcoma. The most common sites of metastases are the liver and lungs, followed by the skin, soft tissue, bone, and brain. Autopsy findings suggest metastatic involvement of the lung (80%), bone (40%), liver (39%), peritoneum (19%), and brain (16%). These tumors can occasionally involve regional lymph nodes.

4 Clinical Manifestations

Retroperitoneal leiomyosarcoma grows very rapidly but only causes clinical symptoms in advanced stage. Due to the lack of specific manifestations, the tumor won't be identified until it has grown huge in advanced stage. Abdominal mass as the primary symptom in 70% of patients is mostly seen in patients who present with upper abdominal discomfort.

Retroperitoneal leiomyosarcoma in the upper abdomen may compress digestive organs, thereby causing symptoms such as abdominal bloating, abdominal pain, abdominal discomfort, anorexia, nausea, and vomiting. Of them, abdominal bloating is the most common symptom, which is aggravated after meals and even progresses to obstruction. Retroperitoneal leiomyosarcoma in the pelvis can cause difficulty urinating or rectal irritation if it compresses the posterior urethra and rectum or cause pain sensation if it compresses sacral nerve tissue. Clinical manifestations of leiomyosarcoma arising from the inferior vena cava depend on the tumor location within the vessel. For example, a tumor arising from the upper 1/3 segment of inferior vena cava or the upper segment of hepatic veins can cause Budd-Chiari syndrome, characterized by hepatomegaly,

liver failure, jaundice with massive ascites, nausea, vomiting, and lower extremity edema. A tumor originated from the middle segment of the inferior vena cava between hepatic and renal veins may cause right upper quadrant pain and tenderness, as well as renal vein thrombosis, which leads to renal dysfunction, increased BUN levels, or even nephrotic syndrome. Moreover, a tumor originated from the inferior vena cava below the renal vein may cause lower limb edema. Advanced tumor may metastasize to distant sites, resulting in systemic sera symptoms such as cachexia, anemia, and fever.

5 Examination and Staging

It is difficult to diagnose primary retroperitoneal leiomyosarcoma in early stage due to insidious onset, which is mainly detected by physical examination and imaging system. Currently, CT is the most important imaging method for evaluating tumor features and invasion of surrounding structures. Cross-sectional imaging can display tumor size and range, as well as invasion of surrounding organs and blood vessels after injection of contrast medium. Retroperitoneal leiomyosarcoma is usually very large in size, and CT detects a large and heterogeneous mass with irregular borders and a low-density center, suggesting hemorrhage, necrosis, or cystic degeneration, without calcification. The margin of a primary or metastatic tumor may be moderately enhanced. Smaller masses are typically homogeneous. MRI has the advantage in determining involved blood vessels because of multi-axis planar imaging capacity, intrinsic difference in strength of signals, flow-air interface, and flow-enhanced technology. MRI can help accurately localize the tumor and judge the involvement of surrounding structures, which is especially valuable for evaluating tumor boundary, vascular richness, and vascular invasion (Hartman et al. 1992). Leiomyosarcoma originated from major blood vessels may be located inside, outside, or both inside and outside of the lumen, which usually exhibits signals similar to the muscle on T1-weighted images, whereas moderate to high intensity signals on T2-weighted images (De Beuckeleer and Vanhoenacker 1997). Angiography not only demonstrates leiomyosarcoma with rich blood supply but also serves as a useful tool for evaluating major vascular involvement. The diagnostic value of PET-CT remains unclear; however, it may be an alternative choice for clarifying recurrence and metastasis. As a commonly used method, ultrasound can disclose the tumor's location, size, and relationship with major blood vessels, with a certain resolution for predicting the nature of the tumor. Leiomyosarcoma presents with heterogeneous echoes; however, ultrasound is insensitive in detecting lesions located in the intestine, retroperitoneum, or mesentery. Assistance in the diagnosis of liver metastasis detected by CT can be provided by ultrasound, which guides needle biopsy for pathological diagnosis as well.

Clinical staging and determination of the nature of retroperitoneal leiomyosarcoma depend on pathological interpretation. However, it is difficult to set up standard criteria for judging benign vs. malignant nature of leiomyosarcoma. In fact, leiomyosarcoma is a series of lesions varying biologically. Leiomyosarcoma may result from malignant transformation of leiomyoma. Therefore, it is almost impossible to artificially distinguish a malignant tumor from a benign one. Histological grading can be achievable based on indicators such as tumor size, cell atypia, necrosis, and mitotic activity, of which mitotic activity is the most reliable one. A tumor with more than five mitotic/10 HP should be considered malignant, whereas with one to four mitotic/10 HP considered potentially malignant, especially when the tumor is large in size with necrosis and obviously atypical nuclei. Even with this strict criterion, this large tumor cannot be absolutely predicted to be benign.

6 Treatment

6.1 Surgical Resection

Surgical resection is currently the primary means of treating retroperitoneal leiomyosarcoma. Whether the tumor can be completely resected or not will profoundly affect tumor recurrence and patient's prognosis. Prior to the development of operative strategy, if lymphoma, PNET, or other chemotherapy-sensitive tumors cannot be ruled

out, tumor's pathological nature should be confirmed by biopsy with hollow needle under the guidance of ultrasound or CT preoperatively. For a patient who has undergone biopsy, the entire puncture pathway should be removed to avoid tumor metastasis. If complete resection of leiomyosarcoma is considered challenging preoperatively, the patient can receive neoadjuvant chemotherapy based on pathological findings and won't undergo surgery until the tumor has shrunk, in order to improve operational effectiveness.

Leiomyosarcoma located in the retroperitoneum is mostly >10 cm (maximum diameter) in size. The large tumor size and important organs/structure adjacent to the tumor make surgery extremely challenging. To achieve wide resection, combined resection of the small intestine, colon, kidney, suprarenal gland, or pancreas adjacent to the tumor is often required. Another dilemma is that retroperitoneal leiomyosarcoma directly invades major blood vessels and involves partial resection and reconstruction of the inferior vena cava and renal vein. In fact, leiomyosarcoma is usually encapsulated, growing expansively rather than directly invading the surrounding structures. During surgery, the tumor body is more easily separated from the surrounding tissue; however, it is always adherent to major blood vessels. Particular attention should be paid to the separation so as not to tear blood vessels. Some clinicians therefore emphasize that the separation of blood vessels should start from the distal end of the tumor in order to avoid sudden bleeding and to ensure complete removal of the tumor. If the tumor has invaded blood vessels, removal of the specific part of major blood vessels would be safer, and if necessary, revascularization will be performed after the removal of the tumor.

Even after complete resection of the primary tumor, 50% of patients may experience a relapse. Consequently, patients should be closely followed up by CT or ultrasound to detect potential relapse as early as possible. Re-excision is an option for patients with local recurrence. Similar to the first operation, reoperation is indicated for patients without identifiable distant metastasis. Some patients with local relapse may still obtain a long-term disease-free survival after tumor resection.

Retroperitoneal leiomyosarcoma often metastasizes to the liver. As metastatic leiomyosarcoma is resistant to chemotherapy or interventional treatment, the patient's prognosis is dismal, with shortened survival time. For patients with liver metastases, the median survival time does not exceed 14 months. Due to limited treatment options for liver metastases from leiomyosarcoma, the value for resection of metastatic lesion needs to be further explored. Lung metastases from leiomyosarcoma are often multifocal, which should be surgically removed if they are isolated lesions.

6.2 Radiotherapy

Radiotherapy plays a very limited role in the treatment of leiomyosarcoma but exerts palliative effect in some patients. Adjuvant radiotherapy may be considered after lumpectomy.

6.3 Chemotherapy

Leiomyosarcoma is relatively resistant to chemotherapy, and the role of postoperative adjuvant chemotherapy remains unclear. Currently, there is no standard treatment for patients with advanced-stage tumors who have no response to other therapies. Although it cannot cure these patients, chemotherapy may slow down tumor progression. Doxorubicin, epirubicin, liposomal doxorubicin, ifosfamide, or dacarbazine alone, as well as anthracycline-based combinatory regimen, are common palliative protocols for metastatic soft tissue sarcoma. In Phase II clinical trial of gemcitabine plus docetaxel (GT), the progression-free survival (PFS) and overall survival (OS) were 6.2 months and 17.9 months, respectively. GT yields a higher response rate and survival rate for both uterine leiomyosarcoma and non-uterine leiomyosarcoma. Recently, monoclonal antibodies targeting the mTOR signaling pathway, vascular endothelial growth factor (VEGF) receptor, and insulin-like growth factor receptor have shown a certain effect on patients with refractory leiomyosarcoma.

Molecular mechanisms of retroperitoneal soft tissue sarcoma and development of new drugs are attracting more and more attention.

7 Efficacy and Prognostic Factors

The prognosis of retroperitoneal leiomyosarcoma is poor, with postoperative 5-year survival rate of 28–40%. The main factors attributed to worse prognosis of retroperitoneal sarcoma are poor tumor differentiation, postoperative local recurrence, and incomplete removal of the primary and secondary tumor. The recurrence rate of retroperitoneal liposarcoma or leiomyosarcoma is >50%; and 5-year survival rate is only 30% for relapsed cases. The prognosis is dismal in patients who have experienced recurrence and distant metastases of leiomyosarcoma and even worse if the tumor grade index is high or vascular invasion occurs.

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