

A 10-year observational single-center study of retroperitoneal unicentric Castleman disease

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Abstract

Diagnosis of unicentric Castleman disease (UCD) is not easy before the resection and obtainment of pathological result. We retrospectively summarized 10-year experience of clinical evaluation and management for retroperitoneal UCD in Peking Union Medical College Hospital (PUMCH) between December 1, 2009 and December 31, 2019. Seventy two UCD patients with pathological diagnosis after resection were screened out. Among them 25 patients had retroperitoneal UCD. The average age of the 25 patients was 43.80 ± 12.79 , and 52.00% were male. No patients had systemic symptoms, and 1 patient got preoperative treatment. The average size of masses was 5.59 ± 2.86 cm. The UCD sites included kidney, adrenal area, perinephric area, pancreas, peripancreatic area, area of descending part of duodenum, periaortic area or beside iliac artery, and others. The masses presented different degree of enhancement on CT scans and hypoecho or isoecho on ultrasound. Increased metabolism could be found on ^{18}F -fluorodeoxyglucose positron emission tomography-computed tomography (^{18}F -FDG PET/CT). Some patients had positive results on somatostatin receptor imaging, but none had positive results on ^{131}I -metaiodo-benzylguanidine (^{131}I -MIBG). Some patients presented the elevated level of interleukin-6 (IL-6), 24hour-urinary catecholamine and tumor markers. All the patients received complete resection of masses and 96.00% had hyaline-vascular type pathology except 1 patient (plasma cell-type). Ninety two percent patients received a long-term follow-up with an average follow-up time of 35.48 ± 33.90 months. No patients died or experienced relapse during follow-up. Differential diagnosis of retroperitoneal UCD may be difficult according to imaging and laboratorial examinations. Differential diagnosis with pheochromocytomas/paragangliomas should be taken into special consideration. Different imaging examinations, such as CT/MRI, ^{18}F -PET/CT, somatostatin receptor imaging and ^{131}I -MIBG, can be combined for differential analysis. Complete resection is the best treatment and could provide a final pathological diagnosis.

Abbreviations: ^{131}I -MIBG = ^{131}I -metaiodo-benzylguanidine, ^{18}F -FDG PET/CT = ^{18}F -fluorodeoxyglucose positron emission tomography-computed tomography, AFP = alpha fetoprotein, CD = Castleman disease, CT = computed tomography, HV = hyaline-vascular, IL-6 = interleukin-6, MCD = multicentric Castleman disease, MRI = magnetic resonance imaging, PC = plasma-cell, SUVmax = maximum standardized uptake value, UCD = unicentric Castleman disease.

Keywords: diagnosis, long-term follow up, resection, retroperitoneal, unicentric castleman disease

Editor: Wen-Wei Sung.

HL contributed equally with corresponding author.

The study was approved by the Ethics Committee of Peking Union Medical College Hospital (Beijing, China).

Consent for publication was obtained from all the authors.

The authors have no conflicts of interests to disclose.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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How to cite this article: Wang W, Dong D, Wen J, Li H. A 10-year observational single-center study of retroperitoneal unicentric Castleman disease. *Medicine* 2021;100:10(e25088).

Received: 6 May 2020 / Received in final form: 18 January 2021 / Accepted: 17 February 2021

<http://dx.doi.org/10.1097/MD.00000000000025088>

1. Introduction

Castleman disease (CD) was firstly described by Benjamin Castleman in 1956. It is a rare, heterogeneous group of hyperimmune lymphoproliferative disorders.^[1] There are 3 basic histopathologic subtypes: hyaline vascular (HV), plasma cell (PC), and mixed variant. There are also 2 different clinical entities: the unicentric type and multicentric type.^[2] Unicentric Castleman disease (UCD) is a localized disease which presents with isolated enlarged lymph nodes with no obvious systemic symptoms, and multicentric Castleman disease (MCD) is a serious systemic condition.^[3] The multicentric type usually presents generalized lymphadenopathy, constitutional symptoms, organomegaly and more aggressive clinical course with the potential for malignant transformation.^[2] UCD is usually detected on radiological imaging incidentally or detected by a symptomatic lymph node mass. However, diagnosis of UCD is not easy before the resection and obtainment of pathological result.

The diagnosis of CD should be considered only after other common causes of lymphadenopathy have been ruled out.^[2] In addition, UCD is easily misdiagnosed as other solid tumors. Imaging examinations are important for diagnosis and treatment. However, the low incidence of the disease has led to a limited analysis of its imaging characteristics.^[4] According to existing studies, some features were summarized, but differential

diagnosis with other solid tumors are usually difficult without pathological analysis.^[5,6] The reports of some special imaging examinations are relatively few. Furthermore, the optimal treatment of CD is unknown. However, surgery alone appears to be definitive therapy for subsets of patients. Our principal purpose is to discuss if surgical resection is sufficient for achieving cure and excellent long-term outcome in patients with retroperitoneal UCD. Here we summarized our 10-year experience of clinical management for retroperitoneal UCD patients and provided some more information for differential diagnosis of UCD with different imaging examinations.

2. Methods

2.1. Study design and participants

This was a single-center, retrospective, observational study. We retrospectively analyzed the clinical data of retroperitoneal UCD patients who underwent surgery in Peking Union Medical College Hospital (PUMCH) from December 1, 2009 to December 31, 2019. We would like to summarize the examination methods for differential diagnosis and the long-term prognosis of UCD patients. The screening process was shown in Figure 1. The exclusion criteria included:

1. the patients who just experienced “mass biopsy”;
2. the patients who had the diagnosis of MCD before or after surgery.

Our study was approved by the Ethics Committee of PUMCH. Informed consent was obtained from all patients.

2.2. Treatment and follow-up

All the included patients underwent retroperitoneal mass resection successfully. We obtained baseline data of all the patients before treatment. Pretreatment, abdominopelvic com-

puted tomography (CT)/ magnetic resonance imaging (MRI), ultrasonography, ¹⁸F-fluorodeoxyglucose positron emission tomography-computed tomography (¹⁸F-FDG PET/CT), ¹³¹I-metaiodo-benzylguanidine (¹³¹I-MIBG) imaging, and somatostatin receptor imaging were obtained in the patients. If the patients performed laboratorial tests of tumor markers, such as carbohydrate antigen and alpha fetoprotein (AFP), 24 hours-urinary catecholamine and interleukin-6 (IL-6), the results were also recorded. The main outcomes included long-term survival rates and recurrence rates. Outpatient or telephone follow-up for all the patients were arranged to supplement the long-term outcome information. For evaluating relapse, abdominopelvic imaging examinations were performed during follow-up.

2.3. Statistical analysis

All statistical analyses were performed using SPSS22.0 software (International Business Machines Corporation, Chicago, IL). Data were expressed as means ± standard deviation (mean ± SD) or n (%) as appropriate.

3. Results

3.1. Baseline characteristics

In total, 260 patients with discharge diagnosis of CD were retrieved during December, 2009 to December, 2019 in PUMCH. Among the patients, 72 UCD patients underwent “isolated mass resection” with the pathological diagnosis of “Castleman Disease.” The masses of 22 patients were superficial, 13 were thoracic, 12 were intraperitoneal, and 25 were retroperitoneal. The detailed distribution was shown in Figure 1. The characteristics of patients with retroperitoneal UCD at baseline were shown in Table 1. One female patient who underwent an incomplete resection in another hospital took

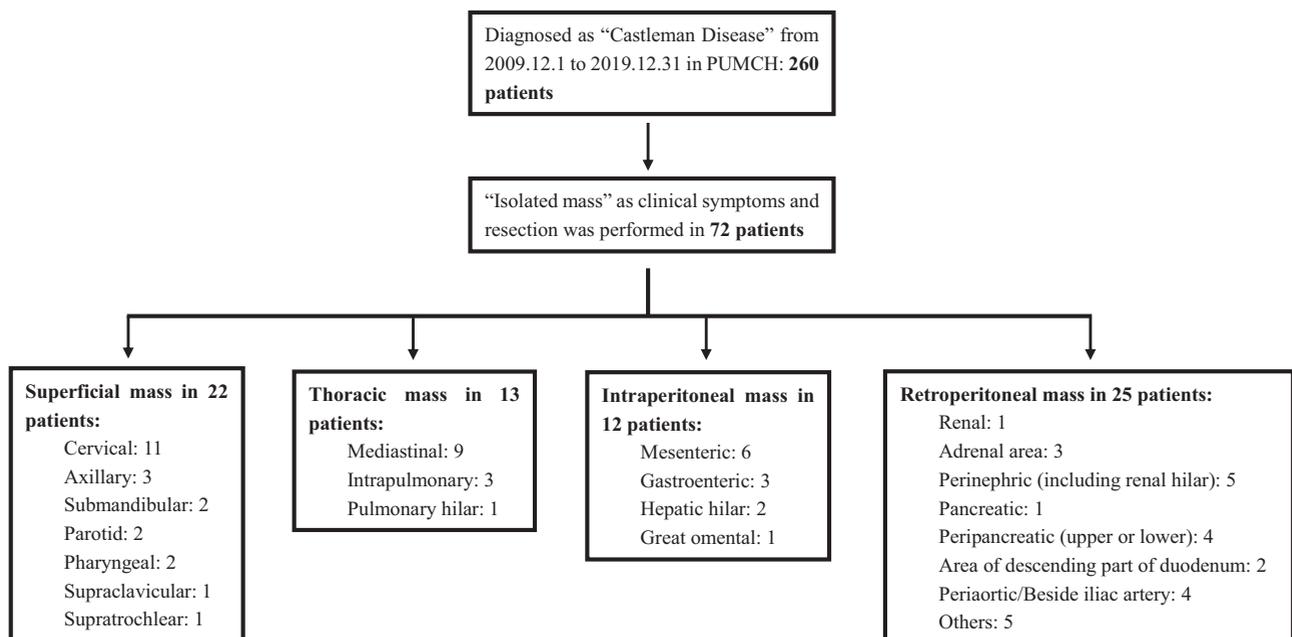


Figure 1. The flow chart of patient filtration and the site distribution of UCD.

Table 1**Characteristics of included retroperitoneal UCD patients.**

Age (yr, M±SD) (Median, range)	43.80±12.79 (43, 23–75)
Gender	
Male	13 (52.00%)
Female	12 (48.00%)
Complications	
HTN	3 (12.00%)
DM	2 (8.00%)
α-thalassemia	1 (4.00%)
Systematic manifestations	0
Pre-operative treatment for CD	1 (4.00%)
Site	
Renal	1 (4.00%)
Adrenal area	3 (12.00%)
Perinephric (including renal hilar)	5 (20.00%)
Peripancreatic (upper or lower)	4 (16.00%)
Pancreatic	1 (4.00%)
Area of descending part of duodenum	2 (8.00%)
Periaortic/Beside iliac artery	4 (16.00%)
Others	5 (25.00%)
Size (cm, M±SD) (Median, range)	5.59±2.86 (4.8, 2.5–13.8)

cyclophosphamide, dexamethasone, and thalidomide before the second operation.

3.2. Imaging and laboratorial analysis

All the CT scans presented various degree of enhancement, and nonenhanced necrosis area could be found in some cases (Table 2). The characteristics of other imaging examinations have been shown in Table 2. However, no specific manifestations were shown on ultrasound or ¹⁸F-FDG PET/CT. The maximum standardized uptake value (SUVmax) of ¹⁸F-FDG PET/CT ranged from 2.3 to 6.9. Although few patients had positive results on somatostatin receptor imaging, no case had positive results on ¹³¹I-MIBG. For serological tests, 3 patients (3/10) had an elevated level of IL-6. One patient with mild higher IL-6

Table 2**Radiological and laboratorial features of included retroperitoneal UCD patients.**

CT scan	21
Mild enhancement	2 (9.52%)
Moderate to obvious enhancement	19 (90.48%)
With nonenhanced area	5 (23.81%)
Ultrasound	13
Hypoecho	11 (84.61%)
Isoecho	2 (15.38%)
With anechoic area	3 (23.08%)
¹⁸ F-FDG PET/CT	5
Increased metabolism	5 (100.00%)
Somatostatin receptor imaging	12
Positive	3 (25.00%)
¹³¹ I-MIBG	9
Positive	0 (0%)
IL-6	10
Elevated	3 (30.00%)
24h-urinary catecholamine	14
Elevated	1 (7.14%)
Tumor markers	6
Elevated	3 (50.00%)

(7.8 pg/ml, normal range < 5.9 pg/ml) and 1 patient with moderate higher IL-6 (75 pg/ml) had no systemic symptoms. The latter had the pathology of plasma cell-type CD. The previously mentioned patient who underwent 2 operations had an obvious elevated IL-6 level (251 pg/ml) before the second surgery. IL-6 levels of all these patients returned to normal after resection. One patient had mildly elevated level of 24h-urinary catecholamine (norepinephrine) with no hypertension. In addition, 3 patients had mildly elevated level of tumor markers (CA727, CA125, and CA199 with AFP, respectively).

3.3. Surgery and follow-up

Completed resections for the retroperitoneal masses (Figs. 2 and 3) were successful in all the patients. Eight patients were treated with phenoxybenzamine before surgery because pheochromocytoma/paraganglioma could not be ruled out. The pathologic analysis revealed that most of cases had HV type pathology, but 1 was PC type and 1 was mixed type respectively. The follow-up rate was 92.30% and the average follow-up time was 34.29±33.66 months with a range of 2 to 115 months. No patients underwent post-operative treatment. No relapse or death was found (Table 3).

4. Discussion

According to results of histopathology, CD could be subclassified into 3 types, HV, PC, and mixed types, and also could be subclassified into UCD and MCD on the basis of clinical features.^[2,7] MCD may present as thrombocytopenia, edema, fever, reticuline fibrosis, and organomegaly.^[3] However, UCD patients usually have no symptoms mentioned above. Some patients may present the symptoms of enlarged lymph node's compression. In this study, all of the retroperitoneal UCD patients have no systemic symptoms. UCD can occur at any age with the median age of 30 to 34 years old.^[8] The median age in our study was 43. Most UCD cases (74%–91%) had a pathology of HV type histology but a small part of cases (9%–26%) had the pathology of PC type histology.^[8] Only 1 patient's pathology (4%) was PC type in our study.

A systematic review which includes 278 patients with UCD reports that the common sites include chest (29%), neck (23%), abdomen (21%), retroperitoneum (17%), and others (10%).^[8] However, in our study, the most lesions were found to be retroperitoneal (34.72%) which was followed by superficial (30.55%), thoracic (18.06%), and abdominal (16.67%). In previous studies, unusual sites such as lung, orbits, nasopharynx, spleen, and small bowel have been reported.^[8] In our study, UCD lesions were also found in some rare sites including lung, kidney, small bowel, parotid gland, and pharynx.

For UCD patients, imaging examinations are usually used for the evaluation of diagnosis. UCD may present as a solitary mass with heterogeneous enhancement on CT scan because of hypervascularity of lesions.^[9] Intraleisional calcification may be found in UCD and this may help for differentiating CD from lymphoma.^[10] For MRI, UCD lesions are usually isointense or hyperintense relative to skeletal muscle on T1WI and hyperintense on T2WI.^[11] On ultrasonography, most UCD appear as hypoechoic masses, and peripheral and penetrating feeding vessels can be seen.^[11] On the other hand, ¹⁸F-FDG uptake is usually moderately increased in UCD on PET/CT.^[9,12] However,

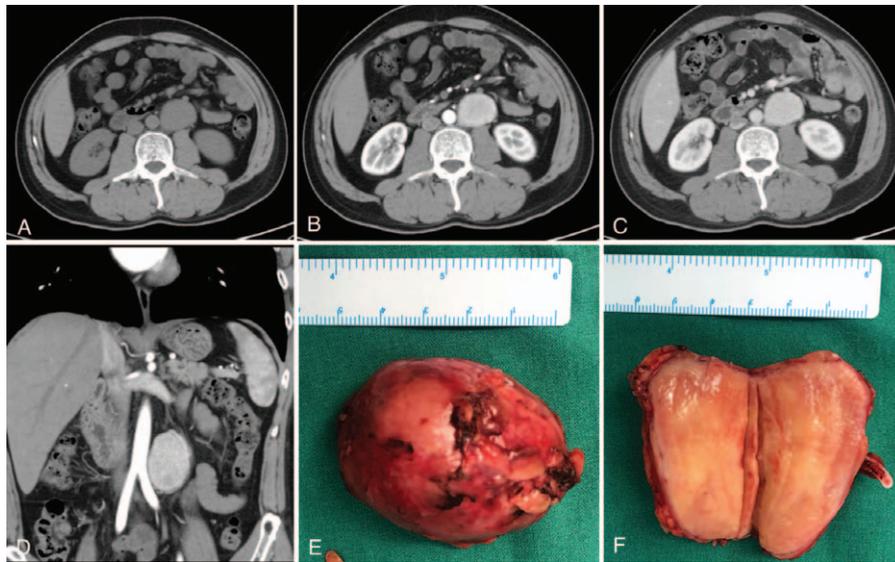


Figure 2. The CT scan (A to D) and gross specimen (E and F) of a periaortic UCD patient. The preoperative CT scan showed that the mass had moderate and uneven enhancement.

all of the imaging manifestations mentioned above are not specific for distinguishing UCD from malignant tumors or neuroendocrine tumors. Because patients with UCD may have no specific symptoms and the incidence of this disease is relatively low, the diagnosis of UCD may be ignored before surgical treatment. The confirmed diagnosis could be obtained from pathological analysis accidentally. Although surgery may be the first choice for these isolated retroperitoneal masses, however, pheochromocytoma/paraganglioma should be considered specially because some pheochromocytomas/paragangliomas are silent. These silent tumors may cause serious hypertension during surgery, and preoperative medical preparation is necessary. Jiang et al^[13] reported that a single retroperitoneal mass with an SUVmax higher than 7.75 on ¹⁸F-PET/CT is more likely to be a pheochromocytoma/paraganglioma rather than UCD. But the SUVmax of UCD could also be as high as 7.7 in this study.^[13] Somatostatin receptor imaging and ¹³¹I-MIBG are usually used for pheochromocytoma/paraganglioma diagnosis. In our study, 12 patients received somatostatin receptor imaging and 3 patients

had a positive result. Some other studies also reported that UCD could be positive on somatostatin receptor imaging.^[14,15] None of 9 patients who underwent ¹³¹I-MIBG presented a positive result. However, the relatively low sensitivity (56 to 72%) of MIBG imaging in detecting pheochromocytoma/paraganglioma should be noted.^[16,17] One of 14 patients who underwent 24-hour urinary catecholamine test had a mildly elevation of norepinephrine. Thereby, it is difficult to distinguish UCD from pheochromocytoma/paraganglioma according to imaging and laboratorial examinations, and preoperative drug preparation may be unavoidable. ¹³¹I-MIBG may have reference value for differential diagnosis according to our results. When UCD occurs in kidney, pancreas, or periaortic area, malignant tumors should be considered. According to our results, imaging and serological tests are also not useful enough for the differentiation when UCD occurs at the sites above. Further tests are needed to be explored for differentiation in the future.

The preferred resolution for UCD is complete surgical resection,^[9] and the latter could provide the final and gold-

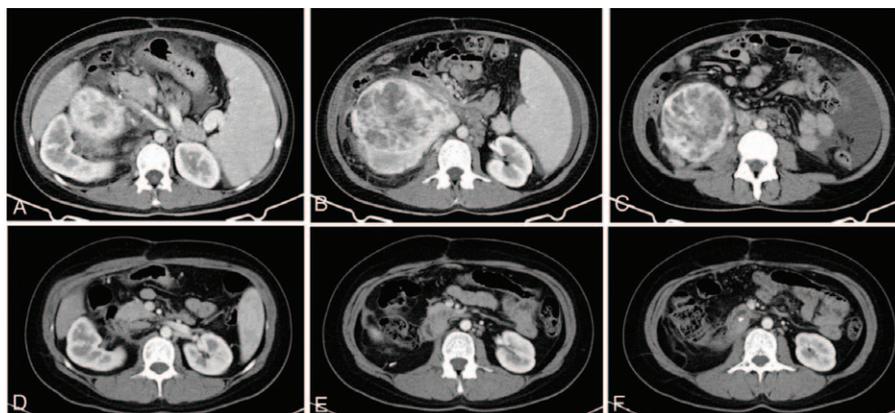


Figure 3. The pre- and post-operative CT scans of the patient who received a second surgery for retroperitoneal UCD (A to C, preoperative; D to F, postoperative).

Table 3**Follow-up of the 25 retroperitoneal UCD patients.**

Pathology	
Hyaline vascular-type	24 (96.00%)
Plasma cell-type	1 (4.00%)
Follow-up	
Follow-up rate	23/25 (92.00%)
Follow-up time (months) (Median, range)	35.48 ± 33.90 (22, 2~115)
Post-operative treatment	0
Relapse	0
Death	0

standard diagnosis for UCD. Ten-year overall survival rates of UCD patients with a complete resection may be more than 95%.^[9] In patients with unresectable lesions, radiotherapy may offer a good long-term response rate as overall survival of 82% at 20 months.^[18] HV-type pathology may lead to a better prognosis than PC-type.^[19] No patients had relapse or death during long term follow-up in our study. The female patient who received 2 surgeries for retroperitoneal UCD resection also had a stable situation at about 6 months after the second surgery.

There are some limitations in this study. First, this is an observational, retrospective study, and not all the patients had complete medical record for examinations. Second, the sample size was relatively small, and it was hard to provide clear recommendations. Third, the study was conducted in a single center, which would limit its generalizability. Thereby studies with higher quality and larger sample size should be carried out in the future.

5. Conclusions

UCD presents as an isolated retroperitoneal mass, and differential diagnosis may be difficult according to imaging and laboratorial examinations. Differential diagnosis with pheochromocytomas/paragangliomas should be taken into special consideration. Different imaging examinations, such as CT/MRI, ¹⁸F-PET/CT, somatostatin receptor imaging and ¹³¹I-MIBG can be combined for differential analysis. Complete resection is the best treatment for retroperitoneal UCD and could provide a final pathological diagnosis.

Author contributions

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Writing – review & editing: Wenda Wang, Jin Wen.

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