Computed tomography parameters can be used as predictive markers for the improvement of renal function in patients with retroperitoneal fibrosis

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Abstract

Objective

To discover the relationship between computed tomography (CT) parameters of retroperitoneal soft tissue of untreated retroperitoneal fibrosis patients and the variation of renal function after treatment.

Methods

Data were collected retrospectively from 42 patients with established diagnosis of retroperitoneal fibrosis, at the Department of Rheumatology in Peking University First Hospital from May 2009 to April 2015. The demographic information, clinical characteristics, laboratory data, treatment and general therapeutic response were collected. The CT parameters such as radial lines, Hounsfield unit values, radiographic classification at baseline before the initiation of therapy were measured. Then the correlations between baseline CT parameters and clinical data were analysed.

Results

The Hounsfield unit values of venous phase and delayed phase at baseline were negatively correlated with the change of estimated glomerular filtration rate (△eGFR) at the 12th month after the initiation of medications. The baseline transverse diameters of the retroperitoneal soft tissue were larger in the group of eGFR <60 ml/min/1.73 m^2 compared with the group of eGFR ≥60 ml/min/1.73 m^2 at the 12th month, while the vertical diameters and maximum cross-section thickness were not. The baseline transverse diameters were also significantly correlated with the duration of intubation.

Conclusion

The baseline Hounsfield unit values and baseline transverse diameters of soft tissue of untreated retroperitoneal fibrosis patients may be used to predict the renal function after 12 months of therapy.

Key words

retroperitoneal fibrosis, computed tomography, glomerular filtration rate

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Introduction

Retroperitoneal fibrosis (RPF) is an inflammatory syndrome characterised by fibroinflammatory tissue in the retroperitoneum. The aberrant tissue may surround the infrarenal portion of the abdominal aorta, inferior vena cava, iliac vessels and ureter. Moreover, when the ureters are entrapped and obstructed, obstructive uropathy and subsequent renal failure may occur (1-3). About two-thirds of RPF are idiopathic retroperitoneal fibrosis (IRPF), the remaining cases are secondary to other causes, such as drugs, tumours and infections (2, 4). RPF is a relatively uncommon disorder and is predominantly found in elderly men. In a study that lasted for a period of 10 years in the Netherlands, the authors found that the calculated annual incidence of RPF was 1.3/100,000 inhabitants (5). The pathogenesis of RPF is still unclear. Histologically, IRPF specimens showed non-specific chronic inflammation (6) characterised by capillary proliferation and inflammatory cell infiltration in the early stage, followed by a fibrotic process in the later stage (2).

RPF is often accompanied by atypical clinical manifestations such as abdominal pain, back pain, fever, anorexia, anaemia and weight loss. It is also associated with elevation of the erythrocyte sedimentation rate (ESR) and the serum C-reactive protein (CRP) (7). Most importantly, the ureteral obstruction usually results in renal insufficiency or renal failure, which is manifested as the decline of estimated glomerular filtration rate (eGFR).

The therapeutic approaches to RPF have evolved. In the past, the initial approach to RPF required ureteral decompression by surgery or placing ureteric stents in case of ureteral obstruction, but it does not affect the underlying pathologic process or the potential for continued anatomic spread and systemic effects (7). Gradually, medical treatment was tried. Glucocorticoids can effectively inhibit the inflammation and therefore have been widely used in the treatment of RPF (8, 9). Immunosuppressive agents, such as azathioprine, cyclophosphamide, leflunomide, methotrexate, mycophenolate mofetil were also effective in the treatment of RPF (10-13). Tamoxifen therapy has been confirmed to be a safe and viable option in the treatment of IRPF. It brought resolution of symptoms, mass regression and recurrence-free survival (14). Glucocorticoid can be used alone or together with tamoxifen or immunosuppressive agents.

CT has been widely used in the diagnosis and follow-up of RPF. It could provide a comprehensive evaluation of the morphology, location, and extent of retroperitoneal soft tissue. If contrast-enhanced CT were conducted, enhancement may be seen in the earlier stage of RPF (2, 15). The size of the soft tissue could be estimated by measuring the diameters of vertical and transverse lines. Hounsfield units (HU) can represent the x-ray attenuation in CT images. Attenuation values expressed in HU are relative to the attenuation of radiation in water. Positive values represent tissues with attenuation values higher than that of water while negative values represent tissues with lower attenuation values (16). To our knowledge, there has been no study that looks at the association between CT images and the renal function so far. Therefore, in this study we tried to evaluate the value of CT parameters in predicting the improvement of renal function after therapy.

Patients and methods

Forty-two treatment-naïve patients with a definite diagnosis of RPF from the Department of Rheumatology of Peking University First Hospital from May 2009 to April, 2015 were enrolled in the study. The diagnosis of RPF was based on the typical clinical characteristics and CT findings (3). Additional inclusion criteria were as follows:

1. with available baseline CT before the initiation of therapy;
2. with regular follow-up at least at the 6^{th} and 12^{th} month after therapy;
3. received immunosuppressive treatment with initial dose of prednisone 1 mg/kg/day (40~60mg/day) for 3~4 weeks and then tapered at the speed of 10% dose per 10~14 days to a maintenance dose of 5mg per day.

Patients received immunosuppressive

drugs, for instance, azathioprine, leflunomide, cyclophosphamide as well as tamoxifen. Those RPF patients with known underlying causes or a history of malignancy were excluded. This study was approved by Peking University First Hospital Ethics Committee.

Data collected

Demographic information including age, sex, associated comorbidities such as diabetes, hypertension, and hyperlipidaemia was recorded for each patient. Clinical characteristics at baseline, therapeutic drugs and response were recorded. Laboratory data included baseline haemoglobin (Hb), CRP, ESR, creatinine, eGFR, and eGFR at the 6th and 12th month of follow-up. The time points of intubation and extubation of Double J catheters were recorded.

The parameters of CT images were analysed and collected by a doctor experienced in imaging. Certain radial lines were measured:

1. Vertical diameters, the vertical length from the starting layer to the end layer of soft tissue (Fig. 1a).

2) Transverse diameters, the left to right diameter of the maximum cross-section above the aorta iliac bifurcation (Fig. 1b).

3) Maximum cross-section thickness, the distance between the maximum section front edge and aorta antetheca above the aorta iliac bifurcation (Fig. 1b).

In the case of contrast-enhanced CT, it was done at baseline when the patient's renal function permitted, the HU values of the soft tissue mass were recorded, including scan phase, venous phase, and delayed phase. The does of contrast agent was 1.5ml per kilogram body weight for each patients, at a flow rate of 3.5mL/s. The venous phase and delayed phase were set to 45 and 60 seconds post injection.

Patients were then classified according to the extent of the soft tissue mass (10, 17): Class I: the infrarenal aorta and/or iliac vessels were surrounded by soft tissue (Fig. 2a). Class II: the infrarenal vena cava were surrounded (Fig. 2b). Class III: lateral extension of the soft tissue with compression of one or both ureters (Fig. 2c). Class IV: extension of soft tissue to include the renal hilum with compression of the renal artery and/or renal vein (Fig. 2d) (17).

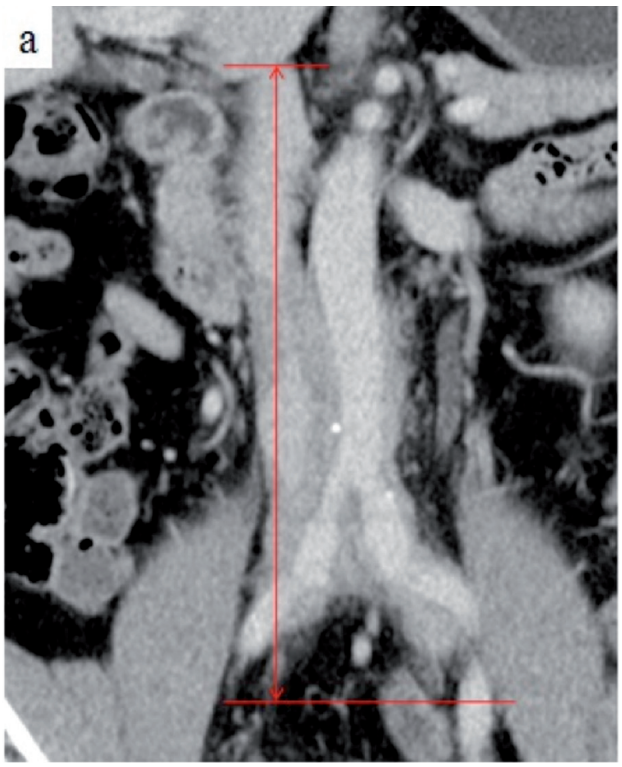

Fig. 1a. Vertical diameters of the soft-tissue, the vertical length from the starting layer to the end layer of soft-tissue (red arrow).

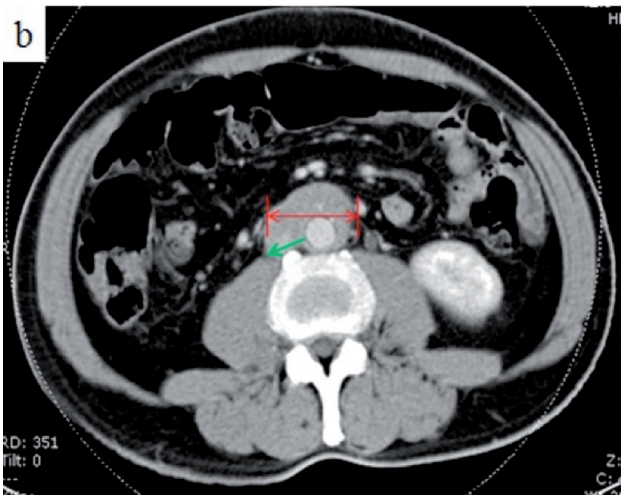

Fig. 1b. Transverse diameters (red arrow) and maximum cross-section thickness (green arrow) of the soft-tissue.

These CT parameters were further analysed together with other clinical and laboratory findings, both at baseline and each follow-up visit.

Statistical analysis

Quantitative data were described as the mean±SD or the median (interquartile range). Differences between continuous variables were analysed by the Mann-Whitney or *t*-test. The correlation of continuous variable were derived from Pearson's correlation coefficients. Chi-square test was used in the correlation analysis of categorical data. A *p*-value of <0.05 was considered statistically significant; all reported *p*-values were 2-sided. The statistical analyses were performed with SPSS software v. 20.0.

Results

General characteristics and symptoms

Out of the 42 patients, 24 (57.1%) were male and 18 (42.9%) were female. The median age was 59 years old (range 36–78) at the diagnosis of RPF. The frequent presenting symptoms were abdominal pain (22 cases, 52.4%), back pain (14 cases, 33.3%), lower extremity oedema (6 cases, 14.3%),

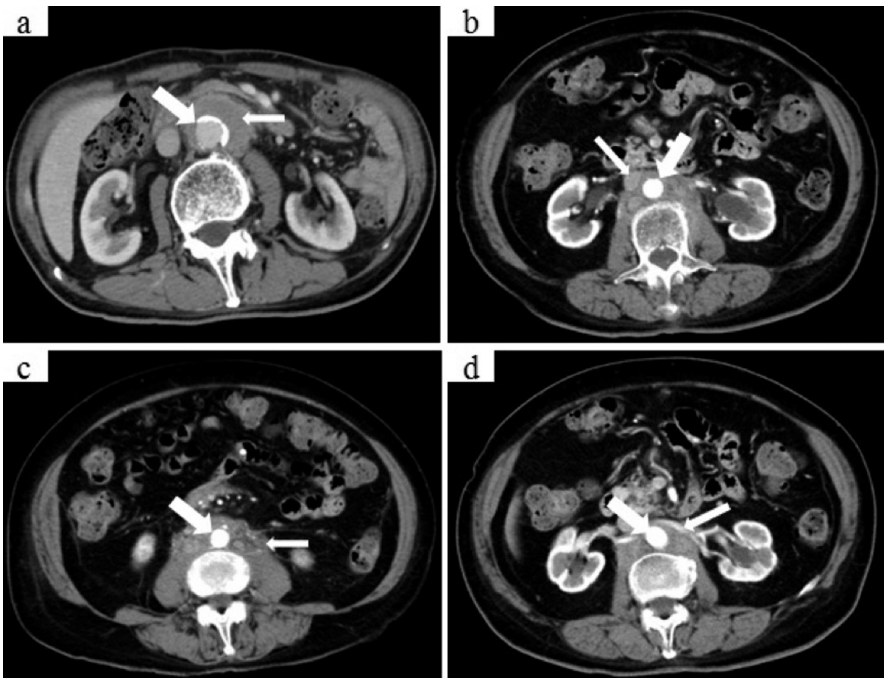

Fig. 2. CT scan of the abdomen with intravenous contrast. (**a**) Large arrow indicates aorta, small arrow indicates soft tissue surrounding aorta. (**b**) Aorta (large arrow) and soft tissue surrounding inferior vena cava (small arrow). (**c**) Aorta (large arrow) and soft tissue surrounding the ureter (small arrow). (**d**) Aorta (large arrow) and soft tissue surrounding left renal vein (small arrow).

weight loss (5 cases, 11.9%), mild fever (4 cases, 9.5%). The duration of these symptoms from occurrence to diagnosis of RPF ranged from 0.33 to 48 months. Among all the patients, 15 cases (35.7%) had known hypertension, 7 cases (16.7%) had hyperlipidaemia, and 5 cases (11.9%) had definite diabetes. Ultrasound of urinary system demonstrated that 34 patients (81.0%) had hydronephrosis and 26 cases (61.9%) had hydroureter on their first visit.

Baseline laboratory findings

At baseline, mean haemoglobin was (126±15) g/L, median CRP was 8.74 (3.64, 53.43) mg/L, the median ESR was 35 (14, 49) mm/h. While the average creatinine level was 121.0 (106.0, 205.0) umol/L, and eGFR was (51.89±24.08) ml/min/1.73 m^2.

Baseline imaging findings

CT findings consistent with RPF were shown in all patients. The mean baseline vertical diameters were (116±48) mm, the mean baseline transverse diameters were (37±14) mm, the mean baseline maximum cross-section thickness were (14±7) mm. Iohexol enhanced CT was done in 24 of all patients since their renal function was permitted. The HU values were 45.83±11.46, 65.23±15.56, 76.75±17.16 in scan phase, venous phase and delayed phase, respectively. The radiographic classification of patients is summarised in Table I. Class I+II+III were seen in the majority (17 cases, 40.5%) of our patients, followed by class I+III (11 cases, 26.2%).

Treatment and general therapeutic response

All the patients received immunosuppressive treatment. The treatment regimens included corticosteroid alone (17 cases), corticosteroid plus azathioprine 100 mg/day (20 cases), corticosteroid plus cyclophosphamide 100 mg/day (3 cases), corticosteroid plus leflunomide 10 mg/day (2 cases). Tamoxifen 10-20 mg/day was extensively used in all these patients. In the 31 patients receiving double-J stent replacement due to acute renal failure secondary to ureteral obstruction, 6 patients had double-J stent removed within 6 months and 12 patients had double-J stent removed within 12 months. The average duration for intubation was 16 (range 2–72) months. The symptoms disappeared at the 6th month visit in all patients. Both

Table I. Baseline radiographic classification of 35 RPF patients.

Radiographic class	n (%)
I	4 (9.5%)
I + II	3 (7.1%)
I + III	11 (26.2%)
I + IV	1 (2.4%)
I + II + III	17 (40.5%)
I + III + IV	1 (2.4%)
I + II + III + IV	5 (11.9%)

CRP and ESR levels were significantly reduced at the 6th and 12th month. Median CRP was 2.79 (1.44, 4.19) mg/L and 1.31 (1.03, 4.00) mg/L, median ESR was 7 (5, 14) mm/h and 6 (2, 10) mm/h at the 6th and 12th month, respectively. Hydronephrosis was detectable in 6 patients, confirmed by ultrasound at the 6th and 12th month visits.

The correlation between baseline CT parameters and eGFR

We defined the △eGFR as the value of eGFR at each follow-up visit minus baseline eGFR. The △eGFR were (12.52±34.37) and (14.29±25.29) ml/min/1.73 m^2 respectively at the 6th and 12th month. Then the correlations between CT parameters and △eGFR were analysed. The results showed that, in those patients who underwent contrast-enhanced CT, the HU value of venous phase and delayed phase at baseline were negatively correlated with △eGFR (r =-0.659, p=0.014 and r =-0.667, p=0.035, respectively) at the 12th month (Table II), however, it failed to reach the statistical significance at the 6th month. There were no correlations between radial lines and △eGFR at the 6th or 12th month. We further studied associations between baseline CT parameters and confirmed renal dysfunction [eGFR <60 ml/min/1.73 m^2] (18, 19). At each follow-up point, patients were stratified into two groups according to eGFR <60 or ≥60 ml/min/1.73m^2 and the CT parameters between two groups were compared. Our data showed that the baseline transverse diameters were larger in the group of eGFR <60 ml/min/1.73m^2 compared with the group of eGFR ≥60 ml/min/1.73m^2 at the 12th month (41.13±12.62 mm *vs*.31.57±9.86 mm, p=0.030). All of the remaining di-

Table II. The correlation between CT parameters and △eGFR during follow-up.

	△eGFR at the 6th month.	△eGFR at the 12th month
HU values (n=24)		
Scan phase	r = -0.304	r =-0.254
Venous phase	r = -0.390	r = -0.659*
Delayed phase	r = -0.384	r = -0.667*
Radial lines (n=42)		
Vertical diameters	r = 0.056	r =-0.014
Transverse diameters	r = -0.161	r = -0.213
Maximum cross-section thickness	r = -0.207	r = -0.135

*$p<0.05$.

ameters were not different between the two groups.

The correlation between CT parameters and the duration of intubation

Thirty-one patients underwent double-J stent replacement due to acute renal failure. Their baseline transverse diameters of the retroperitoneal soft tissue were significantly positively correlated with the duration of intubation (r=0.405, p=0.026). When all CT parameters were stratified into two groups according to median or mean value, none of the CT parameters had an effect on whether patients could have double-J stent removed within 1 year.

Discussion

The symptoms of RPF are mainly related to entrapment and compression of retroperitoneal structures. Due to the lack of specific symptoms and laboratory tests, RPF is frequently diagnosed after severe renal failure has occurred. Thus it represents a challenge for clinicians to early diagnosis and management of RPF (2).

The key role of CT in the diagnosis of RPF was emphasised in several researches (2, 20-23). CT scanning privides a comprehensive evaluation of the morphology, location as well as extent of RPF. Furthermore, it can show the involvement of adjacent organs and vascular structures. Facts proved that CT has become the mainstay of noninvasive diagnosis of RPF (2). Nevertheless, since the value of CT to estimate the renal function outcomes of RPF is unclear, the purpose of our study was to investigate the relationship between CT parameters of retroperitoneal soft tissue of untreated RPF patients and the variation of renal function after treatment.

The usefulness of CT parameters has been widely investigated in other diseases. For example, there was a difference in HU value between negative and metastatic axillary lymph nodes for patients with breast cancer, indicating that the HU measurement could be used to evaluate lymph node metastasis and then to decide preoperative staging (16). Moreover, the length and HU value of kidney stones were independent predictors of successful shockwave lithotripsy in children (24). However, when it comes to RPF, no study has assessed the values of CT parameters in detail. Measuring the diameters and HU value of soft tissue in CT images is a simple and easy procedure.

In our cohort of RPF patients, their baseline characteristics, including the general features and laboratory data, were almost in accordance with previous studies (21, 25). After investigating the baseline imaging changes, we found that the number of patients in Class I+II+III and class I+ III (accounting for 66.7%) was higher than the remaining classes, suggesting that infrarenal aorta and/or iliac vessels and ureters were most frequently involved in this study.

A further analysis of the HU values and improvement of renal function showed that HU values of both the venous and delayed phase at baseline were negatively correlated with △eGFR at the 12th month. It suggested that lower baseline HU values of the venous phase and delayed phase may mean greater possibility of eGFR improvement after one year of treatment. Studies showed that a rapid contrast agent clearance from the kidneys led to a decreasing HU values, on the contrary, a slow contrast agent clearance from the kidneys resulted increased HU values in the same place (26). Therefore, lower HU values of venous phase and delayed phase of retroperitoneal soft tissue may account for relatively rapid iohexol clearance from the kidneys, which means a better recovery of eGFR after therapy.

Then we further stratified the patients into two groups according to eGFR levels at each follow-up time point in order to discover whether there was any difference in the baseline size of retroperitoneal soft tissue. The data demonstrated that the patients with eGFR <60 ml/min/1.73 m^2 at the 12th month had larger baseline transverse diameters compared with the group of eGFR ≥60 ml/min/1.73 m^2. It pointed out that larger baseline transverse diameters may point to difficulty of renal function recovery after one year of treatment.

We also found that baseline transverse diameters were significantly correlated with the duration of intubation, which indicated that patients with longer transverse diameters may need a longer duration of intubation. Possible reasons for that can be interpreted as follows: the greater the transverse diameters, the more likely urinary system involvement. On this occasion, the requirements for intubation emerged.

Our data, for the first time, has shown the correlation between the CT parameters and renal function of RPF, which will contribute to clinical practice in the future. We acknowledge some limitations in this study. Firstly, the nature of a retrospective study meant that certain information was unavailable or incomplete. Secondly, the small size based on the low incidence of RPF limits the representativeness of the results. Hence, larger prospective studies would provide more accurate and convincing conclusions.

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