Comprehensive assessment and outcomes of patients with chronic periaortitis

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Abstract

Objective

Chronic periaortitis (CP) is a less known but more frequently diagnosed fibro-inflammatory disorder, but we know little about it and data regarding follow-up and outcome are still very limited. This study aims to identify the clinicopathologic, laboratory, and radiologic features, as well as outcomes of CP patients.

Methods

Patients with CP from HUVAC database were included in the study. CP was diagnosed based on compatible imaging findings and histopathological evaluation (if available), in addition to clinical findings. Demographics, laboratory, clinical, and imaging data were retrospectively reviewed from medical records.

Results

A total of 51 (male/female:37/14) patients were included in the study. Median (IQR) age was 63 (53-69) years and follow-up duration was 40 (4-60) months. 32 of the patients were IgG4-related CP. The most common form of CP in our cohort was idiopathic retroperitoneal fibrosis (82%), followed by inflammatory abdominal aortic aneurysms (12%) and peri-aneurysmal retroperitoneal fibrosis (8%). 8 (15.6%) patients had thoracic periaortitis and 16 (31.6%) venous involvement. Cyclophosphamide (CYC) combined with steroids was the most preferred treatment modality (43%), followed by rituximab (RTX) (31.3%). Follow-up imaging was done after a median (IQR) of 7 (3-11) months, 30% of the patients were stable and 64.1% showed regression. A total of 18 (35.2%) had been taken off therapy at the last visit.

Conclusion

Idiopathic retroperitoneal fibrosis was the most frequent presentation, whereas 15.6% of patients had thoracic involvement. Venous involvement was also not uncommon. Optimal time for follow-up imaging was determined as 6–9 months. Steroids along with CYC/RTX had a favourable outcome in the treatment of these patients.

Key words

chronic periaortitis, idiopathic retroperitoneal fibrosis, IgG4-RD, vasculitis, rituximab

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Introduction

Chronic periortitis (CP) is a prototypical fibro-inflammatory disorder and is characterised by fibro-inflammatory tissue spreading from the abdominal aorta and iliac arteries into the surrounding retroperitoneum (1). It often encircles the abdominal aorta and iliac arteries; however, it may also affect the subdiaphragmatic arteries, the thoracic aorta, the coronary and supra-aortic arteries (2, 3). Improvement of imaging modalities and their increased usage, along with awareness of retroperitoneal fibrosis (RPF) could have had an impact on the increase in the number of new cases. However, insidious disease onset and lack of typical clinical features creates difficulties in early diagnosis and leads to delay of treatment. Furthermore, many aspects of this rare condition still need to better described. Data regarding supradiaphragmatic and possible venous involvement is limited (4-6).

In this study, we aimed to present the experience of our multidisciplinary center including detailed clinical, imaging, histopathological features, treatment and outcome data.

Patients and methods

The Hacettepe University Vasculitis Research Center (HUVAC) prospective database was established in 2014 and patients diagnosed with vasculitides, according to the 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides and vasculitis mimickers, have been prospectively registered in this database (7). Before registration, all patients provided written consent to participate in the HUVAC database. The study was approved by the Hacettepe University Ethical committee (GO 21/198). Fifty-one, of a total of 2430 patients registered between October 2014-April 2021, were included in this study (Fig. 1). Vasculitis-mimickers (atherosclerosis, peripheral vascular disease, malignancies, tuberculosis, syphilis and other infections), Takayasu's arteritis (ACR 1990 criteria) and Giant Cell Arteritis (ACR 1990 criteria) were excluded (8-10).

This retrospective single-centre study included 51 patients aged ≥18 years diagnosed with CP. The demographic and clinical characteristics, co-morbidities, presenting symptoms, medical treatments and interventions of the patients were retrospectively collected from the HUVAC database and review of medical records. Laboratory tests comprised complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum immunoglobulin G (IgG) level, serum IgG4 level, creatinine, and transaminase levels. Renal failure was defined as decreased glomerular filtration rate (GFR) (estimated GFR <60ml/min/1.73m^2) (11).

Definition of chronic periaortitis and associated conditions

Chronic periaortitis is radiologically defined as idiopathic retroperitoneal fibrosis, periaortic vessel wall thickening, wall enhancement, perivascular soft tissue thickening, and peri-aneurysmal retroperitoneal fibrosis (PRF) (12). CP consists of three clinical conditions as follows: IRF, inflammatory abdominal aortic aneurysms (IAAA), and peri-aneurysmal retroperitoneal fibrosis (PRF) (13). Patients with RPF without aneurysm formation classify as IRF. Patients with aneurysms are categorised as IAAA if ureters are not involved and PRF if inflammatory aortic aneurysms entrap the ureters (14). These definitions were adhered to in our series.

The aetiological classification of chronic periaortitis is as follows: isolated CP, CP associated with other systemic and autoimmune conditions and immunoglobulin G4-related disease (IgG4-RD) associated CP. In our series the diagnosis of IgG4-RD was made based on the 2020 Revised Comprehensive Diagnostic Criteria for IgG4-RD and the pathology of RPF was evaluated based on the consensus statement on the pathology of IgG4-RD (15, 16). Patients were classified as IgG4-related periaortitis if they had either histopathologic findings compatible with IgG4-RD (the presence of the positivity for two of the following three criteria: dense lymphocyte and plasma cell infiltration with fibrosis, ratio of IgG4-positive plasma cells/IgG-positive cells greater than 40% and >10 IgG4-positive plasma cells per high power field when accompanied by typical tissue fibrosis, par-

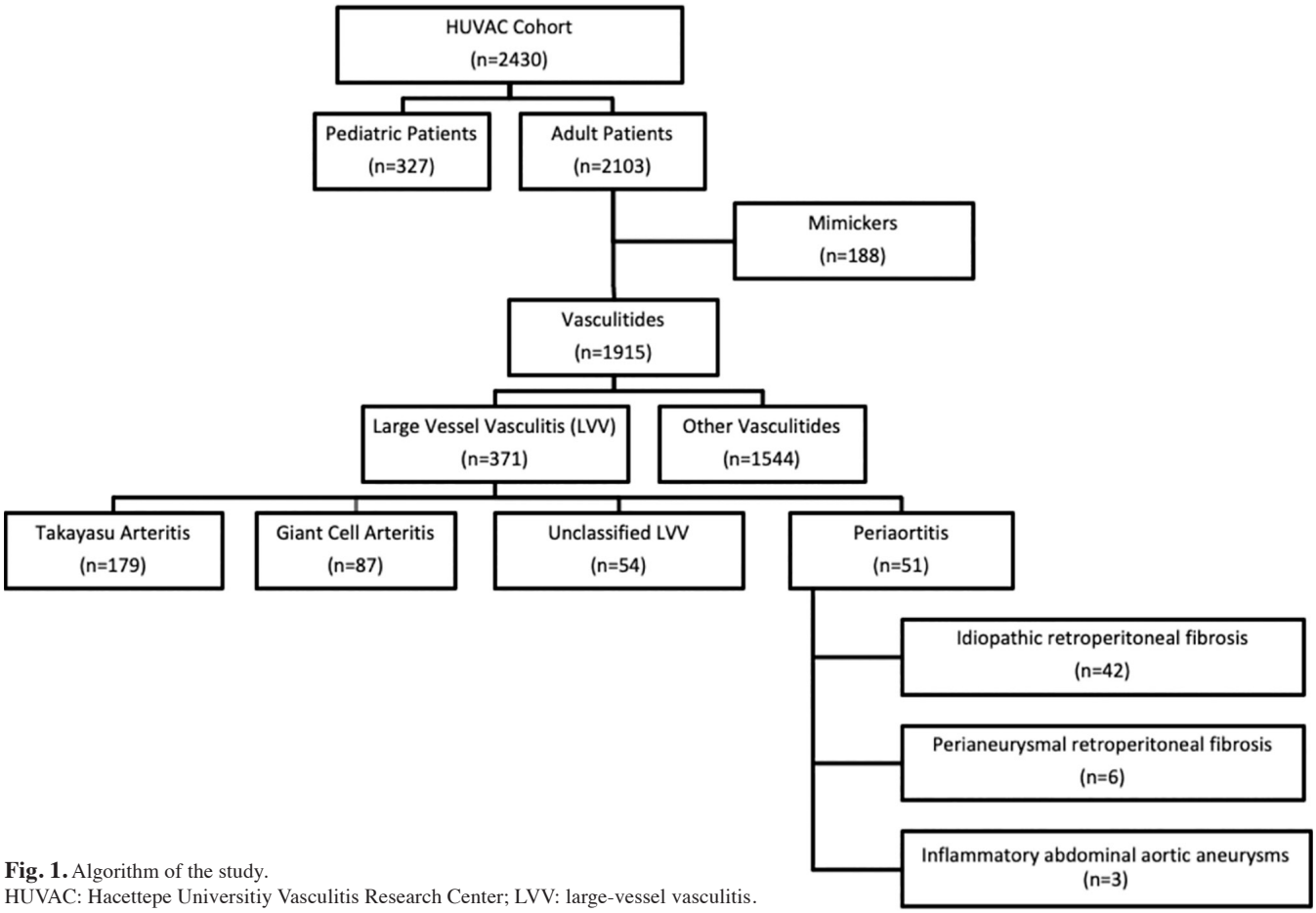

Fig. 1. Algorithm of the study.
HUVAC: Hacettepe Universitiy Vasculitis Research Center; LVV: large-vessel vasculitis.

ticularly storiform fibrosis, or obliterative phlebitis) or elevated serum IgG4 levels (greater than 135mg/dl). RPF due to malignancy (metastasis, lymphoma), drugs (bromocriptine, beta-blockers, hydralazine), radiation therapy and infections were excluded from the study as the term CP only includes idiopathic retroperitoneal fibrosis (17).

Imaging evaluation

Findings on imaging studies with computed tomography angiography (CTA), magnetic resonance angiography (MRA), or positron emission tomography/computed tomography (PET/CT) at the time of diagnosis and follow-up were independently reviewed and interpreted by two vascular radiologists (SA, TH). RPF was accepted as presence of fibro-inflammatory tissue adjacent to the abdominal aorta in the retroperitoneum and the extent of RPF was noted. The aorta and its major branches were assessed for the presence of wall thickening and aneurysm formation. The affected segments were evaluated for length of involvement, wall thickness, type of wall thickness (diffuse *vs*. soft tissue mass-like), the presence of calcification, contrast enhancement, and stenosis. Aneurysm diameters were noted when present. Also, accompanying ureteral and venous involvements were recorded.

Follow-up images were re-assessed for retroperitoneal soft tissue mass size, maximum vessel wall thickness and luminal change, and classified as regressed, stable, or progressed.

Histopathological evaluation

Histopathological specimens from the retroperitoneum were interpreted independently by two pathologists (KK and AS). Immunohistochemical stainings were performed on 4 μm-thick sections using IgG4 (2M49, 1:100) and IgG (polyclonal, 1:10000) antibodies and Leica Bond Max 2 Autostainer.

Treatment and outcomes

Patients' clinical symptoms, physical examinations, laboratory results, and follow-up imaging results were used to evaluate treatment outcomes. All patients' medical treatments [corticosteroids and other disease-modifying antirheumatic drugs (DMARDs)] and interventions (surgical and non-surgical procedures) were examined. Newly diagnosed patients (less than six months follow-up) whose treatment outcomes can not be assessed and patients who didn't have follow-up images were excluded from the outcome analysis.

Radiological disease activity was classified as: regression (decline in existing lesions), stable disease (no change in lesions), and progression (development of a new lesion or progress in existing lesions). Remission signified the absence of clinically active disease together with radiologic remission. Improvement in CP patients meant radiologic regression with no disease activity. Stable disease was defined as disease that had remained unchanged clinically or radiologically. Progressive disease referred to the presence of new clinical or radiological findings.

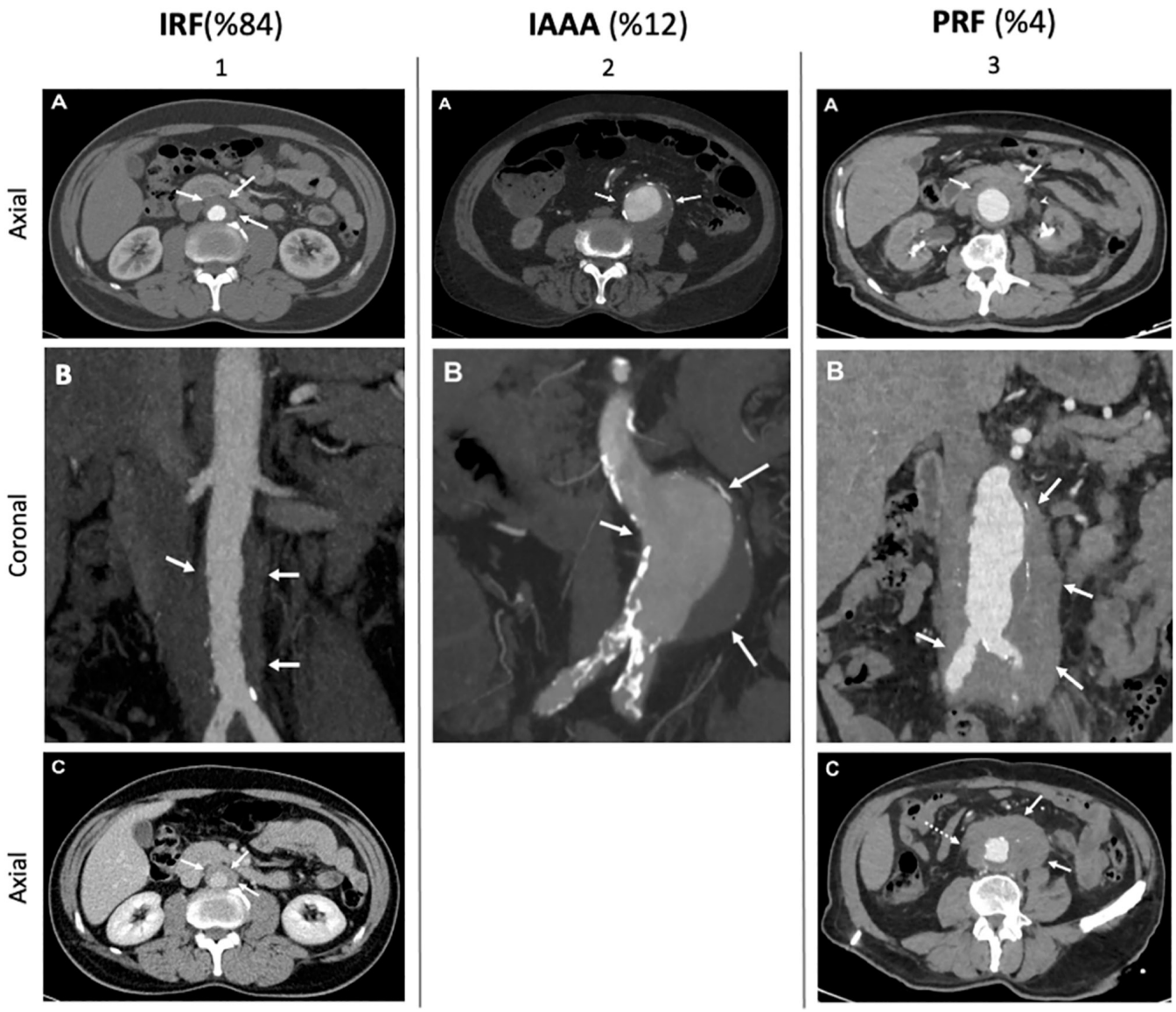

Fig. 2. Types of chronic periaortitis. **1-A**. Axial arterial phase contrast-enhanced CT image shows periaortic soft tissue thickening around the infrarenal abdominal aorta (arrows). **1-B**. Coronal reformatted MIP (maximum intensity projection) image demonstrates aortic wall irregularity and periaortic soft tissue thickening (arrows). **1-C**. Axial CT image obtained in venous phase shows contrast enhancement in perioartic soft tissue (arrows). **2-A**. Axial arterial phase contrast-enhanced CT image shows a partially thrombosed infrarenal abdominal aortic aneurysm (arrows). **2-B**. Coronal reformatted MIP (maximum intensity projection) image better delineates the craniocaudal extension of aortic aneurysm (arrows). **3-A**. Axial arterial phase contrast-enhanced CT image shows periaortic mass-like soft tissue thickening around the abdominal aorta (arrows). Also, bilateral hydroureteronephrosis (arrowheads) and bilateral nephrostomy catheters are observed. **3-B**. Coronal multiplanar reconstructed (MPR) image demonstrates the periaortic soft tissue surrounding the aorta and both common iliac arteries (arrows). Accompanying partially thrombosed aortic aneurysm is also seen. **3-C**. Axial CT image shows that the right ureter (dashed arrow) is retracted medially into the perioartic soft tissue (arrows).
IAAA: inflammatory abdominal aortic aneurysms; IRF: idiopathic retroperitoneal fibrosis; PRF: perianeurysmal retroperitoneal fibrosis.

Statistical analysis

Data was presented as medians/interquartile ranges or numbers/percentages. The variables were investigated using visual (histogram, probability plots) and analytic methods (Kolmogorov-Smirnov) to determine whether or not they were normally distributed. The Chi-square or Fisher's exact tests (when chi-square test assumptions do not hold due to low expected cell counts) were used to compare proportions, where appropriate. Continuous variables were compared using the Mann-Whitney test (non-parametric) and paired t-test (parametric). Paired Student's t-test was used to compare measurements at two different time points (baseline and last visit). The McNemar test was used to compare renal failure at baseline and last visit. A *p*-value of less than 0.05 was considered to show a statistically significant result. Statistical analyses were performed using SPSS (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, v. 24.0. Armonk, NY: IBM Corp.).

Results

Clinical and laboratory findings

Fifty-one patients (73% male) diagnosed with CP were included. The median age at diagnosis was 54 (IQR:46-61) and the median age was 63.0 (IQR: 53.0-69.0) years. The most common presenting symptoms of CP patients were abdomi-

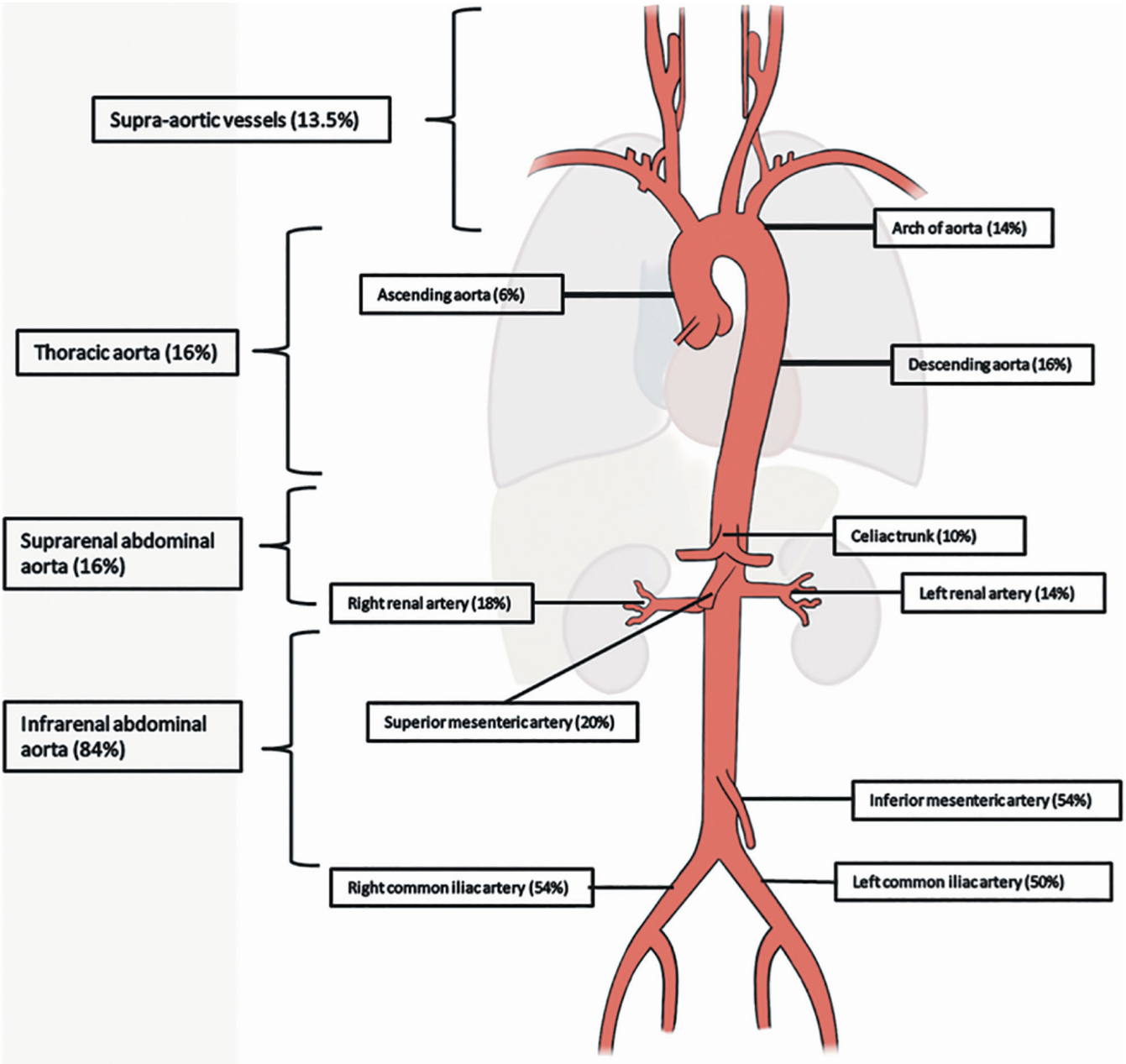

Fig. 3. Vascular involvements in chronic periaortitis patients. The vascular scheme highlights the major involvement sites of chronic periaortitis.

nal pain (35%), flank pain (31%), and back pain (14%). Constitutional symptoms (malaise, fatigue, weight loss, fever) often accompanied these symptoms and were found in 10 patients (20%). 38 patients (74%) had elevated acute phase reactants. Importantly, approximately one-third of patients (14 patients) had renal failure at onset.

31 patients had CP diagnosed in the context of IgG4-related disease, the others were isolated CP patients. 17 CP (33%) patients had at least one comorbidity, mostly hypertension (14%), coronary artery disease (12%), and type 2 diabetes mellitus (8%). Supplementary table S1 gives the baseline demographic and clinical characteristics of the patients.

Radiologic findings in chronic periaortitis

All patients were diagnosed by clinical findings along with imaging modalities, with CTA in 44 patients, MRA in 6 patients, and PET-CT in one patient. Low-density wall thickening or soft tissue masses surrounding the aorta and its major branches were found in 50 (98%) patients. Abdominal aorta involvement consisted of diffuse wall thickening in 23 patients (aortitis) and periaortic soft tissue formation in 21 patients (periaortitis). Wall thickness with contrast enhancement and/or soft tissue masses encircling the infrarenal abdominal aorta was found in 43 patients (84.3%) and extension along the common iliac arteries was present in 29 patients (56.8%), including 3 patients with aneurysms. The suprarenal abdominal aorta was involved in 9 (17.6%) patients, 8 of them also had infrarenal periaortitis.

Periaortic soft tissue masses were expansive, involving the renal pelvis and

ureter in 19 (30%) of these patients. Obstructive uropathy due to compression of the ureters was detected in 13 (25%) patients. Renal parenchymal involvement, renal subcapsular infarction, and bilateral perinephric soft tissue were other urinary system involvements. Pelvic and paravertebral soft tissue masses were found in three patients, two of them also had periaortitis. The most common form of CP in our cohort was IRF. Retroperitoneal masses in the periaortic region without aneurysms (IRF) were detected in 42 CP patients (82%). Six patients (12%) had CP that developed around a dilated aorta without ureteral involvement (IAAA). Inflammatory abdominal aortic aneurysms entrapping the ureter (PRF) were present in 3 patients (6%).

Diffuse periaortitis

Involvement of the abdominal aorta and its branches was present in (almost) all patients with CP, and a minority of patients (15.6%) also had thoracic aorta involvement. Involvement of the decending aorta was present in all patients. Eight patients had diffuse periaortitis, 3/8 had involvement of the ascending aorta and 7/8 the aortic arch. An aneurysm was also present in one patient with ascending aorta involvement.

Patients with thoracic aorta involvement had a significantly higher back pain prevalence (p=0.037). Diffuse CP patients tended to have a higher prevalence of aneurysmal disease (37.5% *vs*. 14.0%) and a greater age at disease onset (59.5 *vs*. 53), although the differences were not statistically significant. There was no difference in gender distribution in both groups (diffuse *vs*. non-diffuse patients), and also similar proportions of patients had systemic symptoms and elevated acute phase reactants.

Diffuse periaortitis was present in 18.8% of IgG4-associated periaortitis/retroperitoneal patients and 10.5% of isolated CP patients. There was no difference between IgG4-related and non-IgG4-related groups in terms of thoracic aorta involvement.

Supra-aortic imaging had been performed and was accessible in 37 patients. 5 patients (13.5%) with diffuse periaortitis (3 IgG4-related CP and 2 isolated CP patients) also had proximal supra-aortic vessel involvements. All of these patients had wall thickening in the left subclavian artery origin, in 2 patients wall thickenings in other supra-aortic artery origins were also detected. In addition, one patient had bilateral vertebral artery, bilateral subclavian artery and axillary artery wall thickening, and occlusion of the right axillary artery. Vascular involvement in CP is given in Figure 3.

Venous involvement in chronic periaortitis

Approximately one-third of the patients (31.3%) had accompanying venous involvement (31.2% in the IgG4-related and 31.6% in the idiopathic CP group, ns). Patients with soft tissue masses in the renal pelvic wall and around the ureter had more frequent venous involvement than those without (52.6% *vs*. 18.8% p=0.014). The most commonly affected vein was the inferior vena cava, 9 patients (56.2%) had peri-caval fibrosis. Renal veins (37.5%) and superior mesenteric veins (18.7%) were the other commonly involved venous structures.

Venous involvement in CP patients was due to external compression of masses around the vessel walls, and in some patients, the lumen diameter was also affected. In 16 patients with venous involvement, 43.7% had a decrease in luminal caliber and 18.7% had occlusion. Distributions of venous involvement, lumen diameter, and additional lesions in patients with venous involvement are given in Table I.

Histopathology

Due to ineligibility for biopsy, risk of bleeding, or patient request, biopsies were not obtained from 32 cases. Pathological evaluation findings of retroperitoneal biopsies were available for 19 patients with CP (10 IgG4-related CP, 9 isolated CP patients). Fibrosis, accompanied by scant mononuclear inflammatory cell infiltration, was the predominant finding in retroperitoneal biopsies of isolated CP patients (Fig. 4). The storiform fibrosis seen in IgG4-related RPF patients was often associated with prominent lymphoplasmacytic inflammation. Five patients had $IgG4^+/IgG^+$ plasma cell ratio of >40%. Histopathological documentation apart from those with retroperitoneal involvement was available in 9 patients (IgG4-related CP patients) and was compatible with IgG4-RD.

Diagnostic criteria for IgG4-related periarteritis/retroperitoneal lesions

Of the 32 patients with IgG4-related CP, 12 patients (37.5%) were classified as definite, 10 patients (31.2%) as probable, and 7 patients (25%) as possible, according to the proposed clinical diagnostic criteria for IgG4-related periarteritis/retroperitoneal lesions. None of the isolated CP patients were classified as definite. Fifteen patients (78.9%) were classified as non-diagnostic. Three isolated CP patients (15.8%) had probable, one had (5.3%) possible diagnosis. Diagnostic criteria for IgG4-related periarteritis/retroperitoneal lesions are given in Figure 5 (18). These proposed clinical diagnostic criteria for IgG4-related periarteritis/retroperitoneal lesions have 90.6% sensitivity and 78.9% specificity in distinguishing IgG-related CP from isolated CP.

Follow-up, treatment and outcomes

Treatment responses were assessed in 39 patients (9 patients were lost to follow-up and 3 patients had a diagnosis of less than six months duration). There was a significant decrease in mean (±SD) ESR [45 (±22) mm/h *vs*. 18 (11)] mm/h, p=<0.001] and CRP [5.2 ± (8.5) mg/dL *vs*. 0.8 ± (0.1) mg/dL, p=0.011] during follow-up. Laboratory and clinical parameters of the patients at baseline and last visit are outlined in Supplementary Table S2.

Thirty-nine patients, with a follow-up of at least six months, were evaluated for treatment response. Three patients (7.7%) were followed up without treatment due to inactive disease. The most preferred induction treatment regimen was cyclophosphamide combined with corticosteroids (43.6%). Two-third of the patients in the cyclophosphamide group had remission/clinical improvement and the rest of them remained

Table I. Distributions of venous involvement in chronic periaortitis patients.

	Location of venous involvement	Lumen diameter	Additional lesions besides arterial involvement/chronic periaortitis
#1	Inferior vena cava, bilateral common iliac veins, left renal vein	Occluded (Inferior vena cava, bilateral common iliac veins, left renal vein)	-
#2	Superior mesenteric vein, splenic vein	Occluded (Superior mesenteric vein, splenic vein)	-
#3	Superior mesenteric vein	Occluded	Soft tissue mass surrounding the left ureter
#4	Inferior vena cava	Narrowed	Soft tissue mass surrounding both ureters, bilateral hydronephrosis
#5	Inferior vena cava (distal part), left renal vein	Narrowed	Soft tissue mass surrounding both ureters, left hydronephrosis
#6	Inferior vena cava	Narrowed	Soft tissue mass in the portal hilus
#7	Inferior vena cava (distal part), left renal vein	Narrowed	Soft tissue mass surrounding both ureters
#8	Left renal vein	Narrowed	Soft tissue mass surrounding the left ureter, left hydronephrosis
#9	Left common iliac vein	Not affected	Soft tissue mass surrounding the left ureter, left hydronephrosis
#10	Inferior vena cava	Not affected	Soft tissue mass surrounding both ureters, right hydronephrosis
#11	Left renal vein (proximal part)	Not affected	Splenic infarct
#12	Inferior vena cava, bilateral renal vein	Narrowed (Inferior vena cava, bilateral renal vein)	Bilateral perinephric soft tissue masses
#13	Right common, external and internal iliac veins	Not affected	Soft tissue mass surrounding the right ureter, right hydronephrosis
#14	Superior mesenteric vein	Not affected	-
#15	Inferior vena cava	Not affected	Soft tissue mass surrounding the left ureter left hydronephrosis
#16	Inferior vena cava	Narrowed	Soft tissue mass surrounding both ureters

stable. Rituximab (33.3%) therapy was the second most frequent treatment in CP patients. The majority of the patients (92.3%) in the rituximab group had remission/clinical improvement or stable disease. Methotrexate (10.3%) and azathioprine (5.1%) were other medical treatments given in combination with corticosteroids.

We also compared treatment toxicity and serious side effects in the long term, in those receiving and not receiving cyclophosphamide. Of the 39 patients whose treatment responses were assessed, 17 were given cyclophosphamide. In the cyclophosphamide group 2 patients experienced serious infections and in the other group 1 serious allergic reaction was observed with rituximab therapy. We did not observe any malignancies in both groups in the long-term follow-up.

In 33 of 51 patients the serum IgG4 levels before treatment were available. In detailed analysis there was no significant difference in treatment responses between the patients with or without elevated serum IgG4 levels. Discontinuation of treatment was more frequent amongst patients with elevated serum IgG4 levels (65% *vs*. 45%), but this was not statistically significant.

The median duration of control imaging was 7 months (IQR:3-11). 25 patients (64%) achieved remission/clinical improvement and 12 patients (31%) remained stable. One patient who received glucocorticoids and rituximab had progressive disease and one patient in the cyclophosphamide group died during induction therapy because of multi-organ failure caused by heart failure and sepsis.

The median duration of induction treatment was 12 (IQR:6-12) months. After induction therapy, 13 patients were followed without treatment. 24 patients were given maintenance treatment and the median duration of maintenance treatment was 12 (IQR:6-8) months. 9 patients (39.1%) received azathioprine, and 7 (30.4%), 6 (26,0%), and 2 patients (8.7%) received methotrexate, rituximab, and mycophenolate mofetil respectively. First line and maintenance treatments of chronic periaortitis patients are given in Figure 6. Two patients' disease relapsed under methotrexate and mycophenolate mofetil treatment and two patients relapsed after discontinuation of treatment (at 24th and 36th months). Totally 18 (35.2%) had been taken off therapy at the last visit.

All patients with hydronephrosis (15 patients) had a ureteral intervention, 2 of them also had resection of pancreatic masses. One of these two patients had surgical intervention without im-

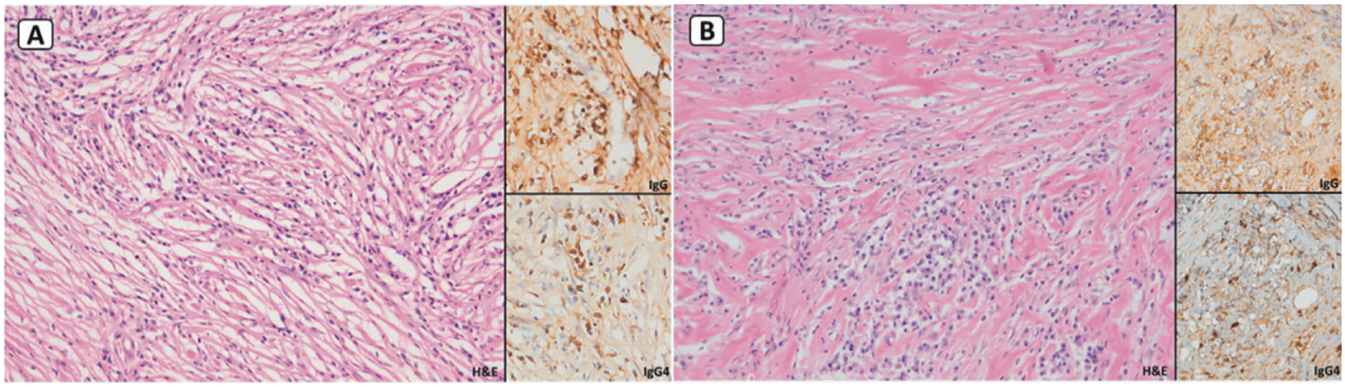

Fig. 4. A. Photomicrograph demonstrating inflammatory infiltrate of lymphocytes and plasma cells within a background of storiform fibrosis. Immunohistochemical evaluation reveals an IgG4/IgG ratio >40%. **B**. Another example with a similar morphology demonstrates IgG4/IgG ratio <40%.

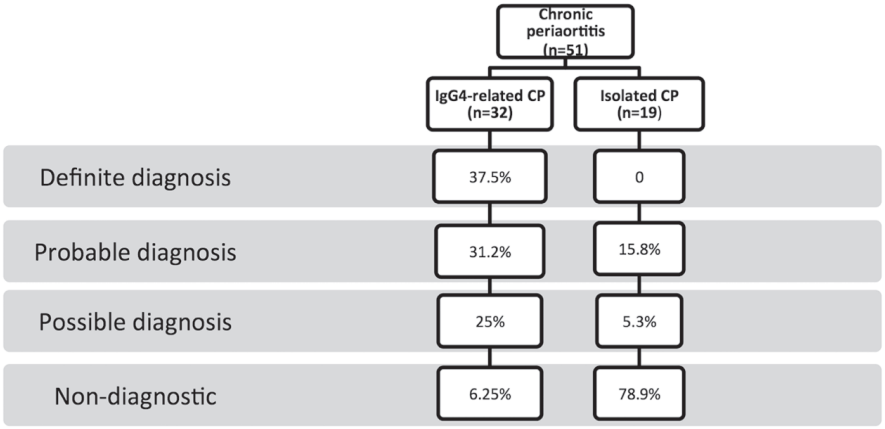

Fig. 5. Diagnostic criteria for IgG4-related periarteritis/retroperitoneal lesions.
CP: chronic periaortitis; IgG4-RD: immunoglobulin4 related disease.

munosuppression, and the other one received additional rituximab and corticosteroids.

Discussion

In this study, we presented the demographic, clinical, radiologic, and laboratory features of 51 CP patients. Patients were mostly diagnosed between the ages of 40-60 and there was a slight male predominance in parallel with previous studies (13, 18). The early signs and symptoms of chronic periaortitis were often non-specific. Abdominal and flank pain, with or without systemic manifestations, was the most common clinical manifestations, as previously reported.

Another important clinical presentation of CP is renal failure due to the compression of the ureters (13, 19). Higher rates of renal insufficiency (46-80%) in IRF patients have been reported in the literature (14, 20, 21). This rate was lower (29.4%) in our study possibly due to the development and widespread use of imaging techniques and early diagnosis. However, approximately one-third of the patients still had renal failure on admission.

Laboratory studies are helpful but not diagnostic in CP (22). Acute-phase reactants such as ESR and CRP are high at onset in more than 70% of patients. Diagnosis is mainly established by radiological examinations such as CTA and MRA as tissue diagnoses may not be available for all patients. Considering that a significant proportion of patients had renal failure on admission, we suggest imaging should be performed in patients with unexplained back or flank pain especially in the presence of elevated acute phase reactants.

Chronic inflammation in the aortic wall and extension to the periaortic space is the hallmark feature of CP. CP, as the name suggests, includes the aorta and its branches. The infrarenal abdominal aorta is the most frequently affected part. Common iliac arteries, inferior mesenteric arteries, renal arteries and superior mesenteric arteries are the other commonly involved sites of the aorta (23). CP not only affects aorta-iliac axis, but also the thoracic aorta and its major branches, even the supra-aortic arteries (2). In the study of 77 CP patients, thoracic aorta involvement was detected in 36% of the patients, a higher rate than in our cohort, however the rate of thoracic aneurysms in diffuse CP patients was similar to ours (24). Diffuse CP patients had more back pain, tended to have more aneurysms and a greater age at disease onset as reported previously, but there was no difference in gender compared to non-diffuse patients. The involvement of supra-aortic vessels was also not uncommon in CP patients (13.5%). Supra-aortic imaging in patients with CP may be rational as it may be important for patients' follow-up and treatment selection.

CP can affect venous structures as well as the aorta and its branches. Venous manifestations of IRF was initially reported as an acute iliofemoral vein thrombosis in a patient complicated by an aortic aneurysm (25). Subsequently, iliocaval complications of RPF, treated with surgery, were described in seven patients (5). To date, several case reports have mentioned retroperitoneal fibrosis and venous obstruction (4, 6, 26, 27). These venous involvements were usually due to compression from periaortic and periureteric masses, and also IRF was reported as a transient risk factor for venous thromboembolism (28). Our series highlights the substan-

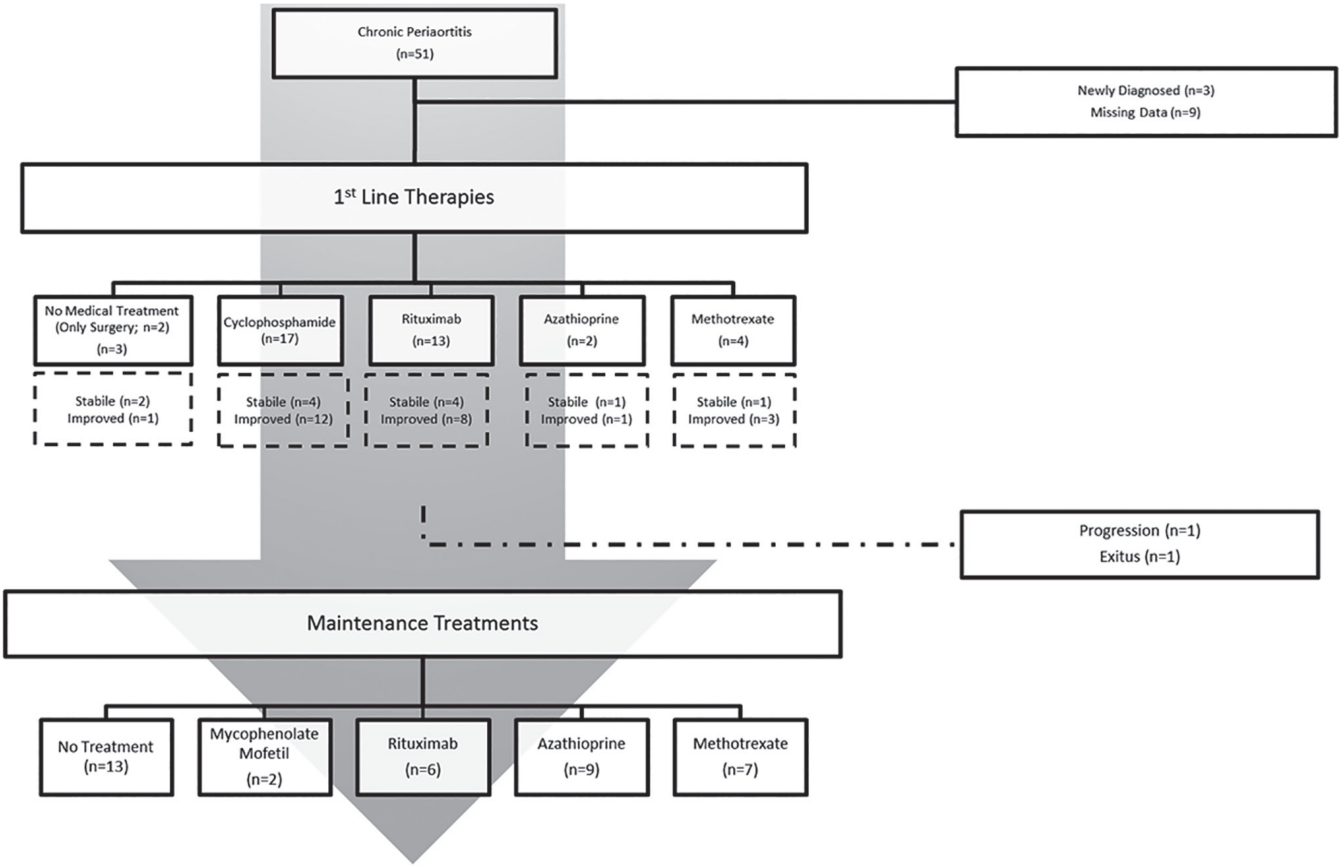

Fig. 6. First-line and maintenance treatments of chronic periaortitis patients.

tial frequency of venous involvement in CP, which affected 30% of the patients. Inferior vena cava, renal veins, and superior mesenteric veins were the most commonly involved venous structures. Venous involvements were due to mechanic or compressive effects of the retroperitoneal masses rather than the inflammation of the vein wall. Although the venous lumen diameter was affected in the majority of patients, almost all patients were asymptomatic. This was probably due to the collaterals that developed over time and overt thrombosis was seen infrequently (14). Although venous involvement is common in patients with CP, it is debatable how useful it is to watch out for them during follow-up.

The diverse and non-specific clinical features of CP alongside its relative rarity frequently leads to diagnostic delay. Specific diagnostic criteria for IgG4-related periarteritis/RPF were established recently, which includes radiologic, laboratory, histologic domains, and additional organ involvement (18). We applied these criteria to our cohort and the majority of the patients with IgG4-related periarteritis/retroperitoneal fibrosis met the criteria. Serum IgG4 elevation may not be detected in all cases with IgG4-related periaortitis (64.5% in our cohort). Considering that biopsy often can not be performed due to complications, the diagnostic criteria developed for IgG4-related retroperitoneal fibrosis/aortitis seems useful.

CP is an immune-mediated disease with a chronic and relapsing nature. The treatment of CP is rapidly evolving and the current first-line treatment for CP is corticosteroids and immunosuppressive agents, the latter usually given to avoid high cumulative glucocorticoid doses (13). But so far, no immunosuppressive agent has been shown to be superior to another, and DMARDs remain poorly studied.

In this study, clinical improvement was achieved in two-thirds of the 19 patients who were given cyclophosphamide. The remainder had stable disease except for the patient who died during induction therapy. Cyclophosphamide was the most commonly preferred agent in our series followed by rituximab (33%). Rituximab resulted in a 61.5% remission rate and 30.7% stable disease, thus seems like a promising therapy in CP patients. Studies on the use of rituximab in the treatment of CP have been reported (29-32). Recently Urban *et al*. reviewed retrospective data of 20 CP patients treated with rituximab. In this trial, the authors showed that rituximab is effective with a 75% remission rate. As with other large-vessel vasculitis, novel therapeutic options are needed in chronic periaortitis, to reduce the side effects of these therapies (33). Tocilizumab, although not given to any of the patients in our series, might be an alternative to current treatments in CP (34).

Reversing ureteral obstruction is another important point in the treatment of CP patients with varying degrees of renal insufficiency. Our work suggests that with early interventions and immunosuppressive therapy, renal failure can

be reversed in the majority of patients.

In our study, the median follow-up duration was 40 months and patients' first imaging was done at 7 (3-11) months. The median duration of induction and maintenance treatment was 12 months each. It is debatable if long-term maintenance therapy is necessary for CP patients. There is paucity of published research studies on how to treat these patients and for how long they should be treated. Though mortality and remission rates have improved over time, there is still a need for optimising CP management to minimise treatment toxicity.

In summary, we presented our experience in CP, especially in terms of vessel involvement, treatment, and outcomes. Our study displayed that despite regular use of imaging modalities renal failure is still an important problem for these patients. However, in the era of new treatment options, better renal results can be achieved. Further studies are required to understand this rare and heterogeneous disease, for making early diagnosis and determining the optimal treatment of patients.

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