IgG4-related aortitis/periaortitis and periarteritis: a distinct spectrum of IgG4-related disease

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Research article

Keywords: IgG4-related disease, aortitis, periaortitis, periarteritis, retroperitoneal fibrosis

Posted Date: March 12th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-16955/v1

Version of Record: A version of this preprint was published at Arthritis Research & Therapy on May 4th, 2020. See the published version at https://doi.org/10.1186/s13075-020-02197-w.

Abstract

Background: Large vessels could be involved in IgG4-related disease(IgG4-RD).This study aimed to clarify the clinical features and evaluate the treatment efficacy for IgG4-RD with aortitis/periaortitis and periarteritis (PAO/PA).

Methods: This study enrolled 587 IgG4-RD patients in a prospective cohort with a follow-up time for more than 6 months. The distribution of IgG4-related PAO/PA was classified into four types: type 1, thoracic aorta; type 2a, abdominal aorta; type 2b, abdominal aorta and iliac artery; type 2c, iliac artery; type 3, thoracic and abdominal aorta; type 4, other arteries. Patient's demographic data, clinical characteristics, laboratory parameters, and treatment efficacy were analyzed.

Results: Of 587 IgG4-RD patients, 89(15.2%) had PAO/PA. The average age was 58.3±11.1 years, with male predominance (85.4%). Vessels affected were as follows: abdominal aorta (83.1%), iliac artery (70.8%), thoracic aorta (13.5%) and other vessels (13.5%). The most prevalent distribution type of IgG4-related PAO/PA was type 2b, with 74 (83.1%) patients, followed by type 2a, type 2c, type 3, and type 1. 55 (61.8%) PAO/PA patients had hydronephrosis, with renal insufficiency occurred in 43 (48.3%), and 31 (34.8%) PAO/PA patients had D-J stent drainage due to severe ureteral obstruction. After treatment with glucocorticoid and immunosuppressants, 82% patients achieved a remission with shrinking of perivascular mass.

Conclusions: IgG4-RD with PAO/PA was distinct from non-PAO/PA in demographic features, organs involvement distribution, inflammatory markers, serum IgG4 and IgE. The most common affected vessel was abdominal aorta, and most patients responded well with treatment.

Introduction

IgG4-related disease (IgG4-RD) is a fibro-inflammatory condition characterized by tumor-like swelling of affected organs, with elevated serum IgG4 and massive infiltration of lymphocytes and plasma cells in involved organs [1–5]. It is a highly heterogeneous disease entity which could affect nearly any organ and often present with multiorgan involvement [6], and the most affected tissues are the lacrimal gland, submandibular gland, lymph node, and pancreas [6–8]. Evidence suggested that IgG4-RD could affect various organs including the vascular system as aortitis/periaortitis/periarteritis (PAO/PA) [9–12], and the most frequently involved blood vessel is the aorta, and medium-sized artery, such as the iliac artery and carotid artery, may be a potential target [5].

PAO/PA was reported to be present in 10–30% of overall IgG4-RD, and they may appear as an isolated lesion of IgG4-RD. Studies had investigated the histopathological diagnosis of the vascular involvement of IgG4-RD, vessel distributions, concomitant non-vascular lesions, treatment efficacy, or potential etiology [5, 10, 13, 14]. However, the lack of large prospective studies may hinder our understanding of the complete clinical picture of IgG4-related PAO/PA because of its heterogeneity. Moreover, early diagnosis and treatment are essential to minimizing irreversible organ damage or unnecessary surgical intervention

[6], such as aneurysmal dilation or rupture of the aorta, or irreversible renal dysfunction due to the obstruction of ureters and hydronephrosis. Therefore, to further understand and achieve better management of IgG4-related PAO/PA, we aimed to analyze the clinical patterns of IgG4-related PAO/PA, distribution of affected vessels, and treatment efficacy.

Methods

Inclusion and exclusion criteria

In our prospective cohort of IgG4-RD carried out in the Peking Union Medical College Hospital (registered as ClinicalTrials.gov ID: NCT01670695), 587 patients were enrolled from January 2011 to September 2018, fulfilling the 2011comprehensive diagnostic criteria [15, 16]. Each IgG4-RD patient had follow-up time of more than 6 months. The diagnosis of IgG4-RD was based on the following criteria: (1) a clinical examination showing characteristic diffuse/localized swelling or masses in single or multiple organs; (2) an elevated serum IgG4 concentration (>135 mg/dL); and (3) a histopathologic examination showing (a) marked lymphocytic and plasma cell infiltration and fibrosis or (b) infiltration of IgG4+ plasma cells (a ratio of IgG4+/IgG+ cells >40% and >10 IgG4+ plasma cells per high power field). Patients with other autoimmune diseases, active/severe infection, malignant disease were excluded. Patients combined with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) were excluded. Patients' affected organs and evaluation of treatment efficacy were determined by clinical symptoms, physical examinations, histological pathology and imaging, including ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography/computed tomography(PET/CT). Allergy history information was collected using the criteria from the European Academy of Allergy and Clinical Immunology（EAACI）. The study was conducted in compliance with the Declaration of Helsinki and was approved by the Ethics Committee of Peking Union Medical College Hospital (No. S-442). All patients signed written informed consent.

Detection of PAO/PA by CT, MRI or PET-CT

A patient was diagnosed with PAO/PA if one or more of the following conditions are present: 1) vessel wall thickening; 2) vessel wall enhancement on contrast imaging; 3) soft tissues around blood vessels with circumferential enhancement on CT or MRI; 3) and ^{18}fludeoxyglucose avidity within a vessel wall or perivascular region on PET/CT[5, 9]. Improvement of PAO/PA was defined as shrinking of perivascular soft tissues and reduced vessel wall thickness. Luminal dilatation at the time of periaortic/periarterial lesion diagnosis was defined as aneurysm, in which the luminal diameter was >1.5 times wider than normal (>45 mm at the thoracic aorta and >30 mm at the infra-renal abdominal aorta) [17, 18]. This study included 89 PAO/PA patients; 8 patients with retroperitoneum lesion but without vessels affected were excluded, patients with malignant tumor during follow up were also excluded. The treatment efficacy was evaluated by clinical characteristics, laboratory parameters, and image of CT scan.

PAO/PA was classified into four types according to the distribution of affected vessels: type 1, thoracic aorta; type 2, abdominal aorta and iliac artery involved, including type 2a, abdominal aorta, type 2b, abdominal aorta and iliac artery, type 2c, iliac artery; type 3, thoracic and abdominal aorta; type 4, other arteries (Figure 1).

Clinical data and laboratory parameters

Patients' data including age, sex, disease duration, history of allergy, treatment strategy, symptom onset, organs affected, and follow-up time were collected. IgG4-RD RI (2015 version) at baseline and each follow-up was evaluated [19]. Laboratory parameters included routine blood analysis; liver function; kidney function; serum IgG, A, and M; serum IgG subclass; total serum IgE; rheumatoid factor, C3 and C4, ESR, and hsCRP tests.

Flowcytometry of $CD19^{+}CD24^{-}CD38^{hi}$ plasmablast/plasma cells

Peripheral blood mononuclear cells from IgG4-RD patients were separated by ficoll gradient centrifugation. B-cell subpopulations were stained with PE-Cy7-conjugated anti-CD19, FITC-conjugated anti-CD24, APC-conjugated anti-CD38 (BD Bioscience, USA). Plasmablast/plasma cell was defined as $CD19^{+}CD24^{-}CD38^{hi}$. Altogether, 93 patients tested $CD19^{+}CD24^{-}CD38^{hi}$ plasmablast/plasma cells at baseline, including 18 IgG4-RD PAO/PA patients and 75 non-PAO/PA patients.

Treatment efficacy assessment

According to comparing image of CT scan before treatment and three months after treatment, the reduction of soft tissue around affected vessels was categorized into three types: 0%–30%, 31%–70%, and >70%.

Treatment response was assessed by evaluating the changes in IgG4-RD RI scores and was divided into complete response (CR), partial response (PR), and no effect (NE, including no improvement or exacerbation). IgG4-RD RI scores<3 and decline of ≥2 were recognized as CR; IgG4-RD RI score decline of ≥2 but remained ≥3 were recognized as PR. If patients' IgG4-RD RI score was 3 points at the beginning, PR was considered a 1-point decrease after the therapy. Patients lacking apparent changes in mass sizes and/or clinical manifestations and IgG4-RD RI score decline of <2 were considered NE[20].Clinical relapse was defined as reappearance of clinical symptoms or imaging findings were worsened with or without elevated serum IgG4 levels[20, 21].

Statistical methods

Statistical analyses were performed using the IBM SPSS Statistics version 24.0 software (IBM, Armonk, NY, USA), Adobe Illustrator CC 2014(Adobe, Cal, USA) and the Prism software version 6.1 (GraphPad Software, La Jolla, CA, USA). Data were reported as means ± standard deviation or median (Q1-Q3). Normally distributed data between two groups were analyzed using independent-samples t-tests or paired-samples t-tests, and a one-way analysis of variance was used to compare groups. Categorical data were analyzed using the chi-square test or Fisher's exact tests, while non-normally distributed data were analyzed using the rank sum test. A two-tailed P-value <0.05 was considered statistically significant.

Results

Demographic characteristics of IgG4-RD with PAO/PA

Among 587 IgG4-RD patients, 89 patients (76 men and 13 women) were enrolled IgG4-related PAO/PA group and 498 patients were enrolled non-PAO/PA group. Of the IgG4-RD patients with PAO/PA, 24 (27.0%) had PAO/PA alone, while other. patients (n=65, 73.0%) had multiple organs involvement Demographic features of IgG4-RD with/without PAO/PA are shown in Table 1. The age of PAO/PA patients was 58.3±11.1 years, with a male/female ratio of 5.85/1. IgG4-RD RI was 10.8±5.3 at baseline. Male patients (59.5±9.7 years) were older than female patients (51.3±16.1 years) at disease onset(*P*=0.015). Moreover, 25(28.1%) PAO/PA patients had allergic history. The median follow-up time was 30(15, 52) months.

Of 89 patients with PAO/PA, 35(39.3%) patients were diagnosed as definite IgG4-RD, 1(1.1%) was probable, 53(59.6%) patients were possible. Nine(10.1%) patients received perivascular mass biopsy, while the rest patients received biopsy from other involved organs, including submandibular gland, lacrimal gland, kidney, lymph node, lung, et al.

Symptoms at disease onset of IgG4-RD with PAO/PA

Symptoms at disease onset in IgG4-RD patients with PAO/PA are shown in Table 2. Pain was the most prevalent symptom observed; among all patients, 57 (64.0%) patients had onset symptoms of back pain (32, 36.0%) and abdominal pain (25, 28.1%). Fourteen patients (15.7%) had lower limb edema. Other onset symptoms included lymph node swelling (22, 24.7%), submandibular gland enlargement (18, 20.2%), cough (11, 12.4%), lacrimal gland enlargement (10, 11.2%), jaundice (8, 9.0%), parotid gland enlargement (5, 5.6%), and nasal congestion (4, 4.5%).

Laboratory parameters of IgG4-RD with PAO/PA

Of IgG4-RD with PAO/PA, serum creatinine increased in 43(48.3%) patients [131(117, 179) μmol/L](Table 3), including 39 (51.3%)male patients and 4 (30.8%) female patients. ESR and hsCRP were 44 (18-75) mm/h and 6.72 (2.14-24.65) mg/L, respectively. Serum IgG, IgG4 and T-IgE were 19.88±8.20 g/L, 4240 (2015,7730) mg/L and 170 (95.3, 463.5) KU/L, respectively.

Comparison of IgG4-RD with/without PAO/PA

Compared with non-PAO/PA patients, PAO/PA patients were older at disease onset, had higher male/female ratio, but had shorter disease duration and lower percentage of allergy history (P<0.001, P<0.001, P<0.001 and P<0.001, respectively; Table 1). The number of organs involved and IgG4-RD RI was comparable in patients with/without PAO/PA. However, patients with PAO/PA had higher percentage of single organ involvement than patients without PAO/PA, P<0.001.

PAO/PA patients had higher percentage of back pain, abdominal pain, and lower limb edema than those with PAO/PA (4.2%, 15.9%, and 1.6%, P<0.001, P=0.005, and P<0.001, respectively). On the contrary, PAO/PA patients had lower percentage of submandibular gland enlargement, lacrimal gland enlargement, parotid gland enlargement, and nasal congestion than those without (42.8%, 45.6%, 13.3%, and 21.3%;P<0.001, P<0.001, P=0.042, and P<0.001, respectively) (Table 2). Consistent with onset symptoms, PAO/PA patients had lower percentage of submandibular gland, lacrimal gland, and paranasal involvement (all P<0.001) (Table 2).

Compared with those with PAO/PA, PAO/PA patients had higher levels of ESR, hsCRP, and IgA(P=0.014, P<0.0001, P<0.0001, and P=0.02, respectively)(Table 3). However, IgG4-related PAO/PA had lower levels of serum IgG4 and IgE levels than those without [8310(3250, 17075) mg/L, 332 (119, 720.5) KU/L;P<0.0001 and P=0.025, respectively)(Table 3). In addition, serum IgG4 levels were higher in patients with PAO/PA and other organs affected [5270(2395, 11910) mg/L] than in patients with PAO/PA only [2418(1583, 4638) mg/L] (P=0.001).

$CD19^+CD24^-CD38^{hi}$plasmablast/plasma cells

Overall, 93 patients were detected of $CD19^+CD24^-CD38^{hi}$ plasmablast/plasma cells at baseline. No statistical significant difference in $CD19^+CD24^-CD38^{hi}$ plasmablast/plasma cell was found between PAO/PA and non-PAO/PA. However, the percentage of $CD19^+CD24^-CD38^{hi}$ plasmablast/plasma was lower in patients with PAO/PA only [2.22%(Q1-Q3, 1.87%-5.90%)] than patients with PAO/PA and other

organ involvement [8.5%(Q1-Q3, 4.52%-16.90%)] or non-PAO/PA[5.58%(Q1-Q3, 2.99%-10.50%)] (*P*=0.015 and *P*=0.023).

Vessels distribution of IgG4 related PAO/PA

Characteristic imaging findings IgG4-related PAO/PA are shown in Figure 2. Of the 89 IgG4-RD patients with PAO/PA, abdominal aorta was the most affected vessel (74, 83.1%), followed by iliac artery (63, 70.8%), thoracic aorta (12, 13.5%), and other vessels, including superior mesenteric artery (6, 6.7%), renal artery (6, 6.7%), common carotid artery (3, 3.4%) and subclavian artery (2, 2.2%), revealing vascular stenosis in 3 patients. Moreover, beside soft tissue around vessels, 27 patients had calcification in the aortic wall, 22.5% of patients had diffuse thickening of the abdominal aortic wall, and 10.1% of patients had aneurysmal dilation of the aorta (Table 4). Abdominal aorta and iliac artery lesions were more common in male patients than in female patients (*P*=0.024 and *P*=0.035, respectively; Table 4). However, the ratio of patients with thoracic aorta and other large vessels affected was higher in female patients than in male patients (*P*=0.048 and *P*=0.004, respectively; Table 4). Besides, female patients had lower percentage of aortic wall calcification than male patients (*P*=0.047; Table 4).

According to the distribution of IgG4-related PAO/PA, type 2, involvement of abdominal aorta and iliac artery, was the most prevalent (74, 83.1%), especially type 2b (52, 58.4%), followed by type 2a (15, 16.9%), type 2c (7, 7.9%), type 3 (7, 7.9%), type 1 (5, 5.6%), and type 4 (3, 3.4%) (Table 4). In addition, no statistical significance in vessel distribution was found between patients with PAO/PA alone and patients with PAO/PA and other organ involvement.

Further, 55 (61.8%) PAO/PA patients had hydronephrosis, including 47(61.8%) male patients and 8 (61.5%) female patients. Caused by ureteral obstruction, 43 (48.3%) patients suffered impairment of renal function. Of patients with severe obstruction, double J (D-J) stent drainage was the first option to relieve obstruction, and 31 (34.8%) PAO/PA patients had D-J stent drainage. With regard to other organs affected, the rates of lymph node, pancreas, submandibular gland, lung, prostate, bile duct, lacrimal gland, parotid gland, paranasal sinus, and thyroid gland involvement were 37.1%, 29.2%, 27.0%, 16.9%, 15.8%, 12.4%, 12.4%, 10.1%, 9.0%, and 2.2%, respectively (Table 2).

Treatment efficacy in PAO/PA patients

PAO/PA patients were treated with glucocorticoids(GCs) or glucocorticoids combined with immunosuppressant agents (GCs plus IM).

Except 18(20.2%) patients received GC monotherapy, other patients were treated with GCs plus cyclophosphamide(CYC) (n=52,58.4%), GCs plus mycophenolate mofetil(MMF) (n=18, 20.2%), GCs plus leflunomide (n=1,1.1%). 41(46.1%) patients were treated combined with tamoxifen (TMX).

After 6 months of treatment, 34 (38.2%) patients achieved reduction of perivascular soft tissues >70%, 39 (43.8%) patients achieved reduction between 31%-70%, and 16 (18.0%) patients had reduction <30%. Compared with male PAO/PA patients, a higher percentage of female patients had reduction of perivascular soft tissues<30%, *P*=0.01. In 31 (34.8%) patients who had D-J stent drainage, 22 (71.0%) patients had successful stent extubating and the median time of extubation was 6 (3-13.5) months. Of 43 patients with renal function impairment, 72.1% patients with renal insufficiency at baseline, serum creatinine normalized during the follow-up. 12(27.9%) serum creatinine decreased but was kept above the normal range.

IgG4-RD RI, ESR, hsCRP, serum IgG4, and IgE levels reduced significantly after treatment. Serum IgG4 returned to normal range in 57.3% PAO/PA patients, and serum IgE returned to normal range in 33.7% patients after 6 months of treatment.

Five (5.6%) patients relapsed during follow-up with median recurrence time 21(15.5-33) months, all of them had two or multiple organs involved at baseline and relapsed in other organ beyond blood vessels. No significant difference in relapse rate was found between male and female patients.

Discussion

To our knowledge, this is the largest prospective cohort of IgG4-RD patients with PAO/PA who were compared to patients without PAO/PA. We compared the clinical manifestations in IgG4-RD patients with or without PAO/PA from a large prospective cohort in China. In addition, the treatment efficacy in PAO/PA patients was evaluated.

IgG4-related PAO/PA has male predominance and could affect multiple organs[10–12], and affects 60%-85%of male patients [10, 13, 22], which was different from Takayasu arthritis (TA) with a young female predominance. Male PAO/PA patients were older at disease onset than female patients. Consistent with other reported IgG4-related PAO/PA, gender has a strong influence on the pattern of vascular involvement and consequently on clinical presentation; women have a higher involvement of supradiaphragmatic vessels, whereas men have abdominal vessel involvement [9, 13, 23].

According to allergy, a substantial percentage of IgG4-RD patients had histories of allergy[8], the percentage of allergy was higher in patients with IgG4-related dacryoadenitis/sialadenitis (DS) than those with non-IgG4 DS [7], and non-PAO/PA patients also had higher percentage of allergy than PAO/PA patients [5]. The demographic features of our PAO/PA patients were consistent with those in other studies [5, 24, 25]. The shorter disease duration indicated that the severe disease activity needs urgent treatment, such as severe constitutional symptoms, back pain, higher inflammatory parameters, or renal function impairment due to ureter obstruction. Whether the low rate of allergy history of PAO/PA patients compared with those without suggested different triggering factors or etiology remained to be further elucidated.

The onset symptoms of PAO/PA patients were non-specific, including pain (often back or abdominal pain, chest or groin pain was relatively rare seen), edema of lower limbs, and dyspnea[26]. In our cohort, the most common onset symptoms were back pain and abdominal pain, followed by lymph node swelling, submandibular gland enlargement, and lower limb edema in most patients with multiorgan involvement. However, back pain or abdominal pain is an atypical symptom, so abdominal CT or MRI must be conducted in patients with such symptoms for early detection of PAO/PA. Of PAO/PA patients, the most prevalent type of vessel distribution was type 2, consistent with Ozawa et al. study [5, 25]. However, PAO/PA patients had much lower rate of DS and paranasal sinusitis compared with non-PAO/PA patients, which is consistent with our previous study that patients without DS had a higher percentage of aorta or larger blood vessel involvement [7].

Elevation of ESR and hsCRP was an indicator of vascular wall inflammation in large-vessel vasculitis, such as chronic periaortitis, Takayasu arteritis, etc. [5, 25, 27, 28]. Our data demonstrated that PAO/PA patients had higher white blood cell count, ESR, and hsCRP, but lower blood hemoglobulin, serum IgG4, and IgE levels, compared with IgG4-RD patients without PAO/PA. Besides, in patients with only PAO/PA involvement, serum IgG4 levels were also lower than those in patients with PAO/PA and other organ involvement [7]. In our cohort, more than 70% of PAO/PA patients had elevated ESR and hsCRP, which is much higher than that reported by Mizushima et al., in which only a small proportion of patients had elevated hsCRP [25]. Patients with only PAO/PA involvement also had low levels of $CD19^{+}CD24^{-}CD38^{hi}$ plasmablast/plasma cells compared with patients with PAO/PA and other organ involvement or non-PAO/PA patients. Circulatory inflammation was prominent, but low serum IgG4 in PAO/PA patients compared with non-PAO/PA patients, indicating different disease pathogenesis which needs to be elucidated. Dacryoadenitis, higher serum IgG4,T-IgE, and higher circulating plasmablasts were risk factors for disease relapse [29–32], and the above parameter was lower in PAO/PA patients which may indicate a lower relapse rate.IgG4-RD with PAO/PA might be a distinct spectrum of IgG4-RD, as it is characterized by prominent fibrosis, sparse lymphoplasmacytic infiltration, fewer extra-nodal germinal centers, and mildly elevated serum IgG1, IgG4, and IgE concentrations [5, 27, 33].

Aortitis needs to be treated urgently because inflammatory aortic aneurysms may have a large diameter or high enlargement rate and are at a high risk of rupture. Patients with chronic periaortitis were often treated with medium to high dose GCs [14, 26]. Immunosuppressants are steroid-sparing treatments for PAO/PA patients. Previous studies indicated that CYC and MMF and rituximab were effective as induction therapy [10, 21, 34, 35]. For patients with ureter obstruction, quick relief from the obstruction by intra-ureteral stenting with a Double-J stent could prevent further kidney damage. If obstruction is absent or mild and there is no renal function impairment, an immunosuppressive regimen is the first option. When moderate to severe ureteral obstruction and/or renal impairment are present, ureteral drainage must be the priority, followed by immunosuppressive therapy [36]. In our cohort, most of the PAO/PA patients were treated with GCs combined with immunosuppressant, and more than 90% of patients achieved CR. More female PAO/PA patients could not achieve reduction of perivascular soft tissues for > 30%, suggesting that female patients tended to be more resistant to treatment than male patients. In

addition, 71.0% of our patients with ureteral obstruction successfully had extubated with a median time of 6 months. The reduction of ESR, hsCRP, serum IgG4, and T-IgE levels was also an indicator of treatment efficacy. Compared with IgG4-DS patients, a higher proportion of PAO/PA patients managed to achieve normal serum IgG4 and IgE levels after treatment [7].

This study had some limitations. First, this is a single-center study. Second, the follow-up time was relatively short. Third, PET-CT is a more sensitive imaging test in evaluating vascular lesions; however, due to its high cost, most of the patients did not undertake PET-CT. Fourth, a more comprehensive investigation of pathogenesis needs to be conducted.

Conclusion

Our study indicates that IgG4-related PAO/PA was distinct from non-PAO/PA in demographic features, organs involvement distribution, inflammatory markers, serum IgG4 and IgE. The most common affected vessel was abdominal aorta, and most patients responded well with treatment. As IgG4-related PAO/PA is a spectrum of fibrosis subtype of IgG4-RD, disease relapse is less likely to occur compared with those without PAO/PA. Our study could promote the understanding of IgG4-related PAO/PA in clinical characteristics and treatment efficacy.

Abbreviations

IgG4-RD: IgG4-related disease; PAO/PA: aortitis/periaortitis and periarteritis; CT: computed tomography; MRI: magnetic resonance imaging; PET-CT: positron emission tomography/computed tomography; IgG4-RD RI:IgG4-RD responder index; D-J stent: double J stent; ESR: erythrocyte sedimentation rate, hsCRP: hypersensitive C-reactive protein; IgG: immunoglobulin G; GCs: glucocorticoids; IM: immunosuppressant; CYC: cyclophosphamide; MMF: Mycophenolate mofetil; tamoxifen: TMX; Takayasu arthritis: TA; IgG4-DS: IgG4-related dacryoadenitis/sialadenitis.

Declarations

Acknowledgements

Not applicable

Authors' contributions

L.P. and P.Z. designed the study, performed data analysis and wrote the manuscript. P.Z. conducted flowcytometry measurement and data analysis. J.L., Z.L. and H.L. collected data. L.Z., X.W., F.T., X.L., H.G.and Y.F. participated in case and data collection. L.Z. helped with radiographic diagnosis. Y.Z., X.Z.

and F.Z helped optimize the research and proofread the paper. W.Z. and Y.F. designed and directed the study and revised the manuscript.

Funding

This work was supported by The National Key Research and Development Program of China [2016YFC0901500], CAMS Innovation Fund for Medical Sciences(CIFMS) [2017-I2M-3-001] and National Natural Science Foundation of China [81771757、81571587 and 81601433].

Availability of data and materials

The dataset analyzed in this paper is available from the corresponding author on reasonable request, and with appropriate additional ethical approvals, where necessary.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Peking Union Medical College Hospital. All patients consented to attend this study and signed a written informed consent.

Consent for publication

Yes, we obtained consent for publication from all authors in the manuscript.

Conflict of interest statement

The authors have declared no conflicts of interest in this work.

References

1 Shiokawa M, Kodama Y, Sekiguchi K, et al. Laminin 511 is a target antigen in autoimmune pancreatitis. *Sci Transl Med* 2018;10(453).

2 Hubers LM, Vos H, Schuurman AR, et al. Annexin A11 is targeted by IgG4 and IgG1 autoantibodies in IgG4-related disease. *Gut* 2018;67(4):728-35.

3 Martin-Nares E, Angeles-Angeles A, Hernandez-Molina G. Major salivary gland enlargement in IgG4-related disease is associated with multiorgan involvement and higher basal disease activity. *Mod Rheumatol* 2019:1-5.

4 Deshpande V, Zen Y, Chan JK, et al. Consensus statement on the pathology of IgG4-related disease. Modern pathology : an official journal of the United States and Canadian Academy of Pathology, *Mod Pathol*. 2012;25(9):1181-92.

5 Ozawa M, Fujinaga Y, Asano J, et al. Clinical features of IgG4-related periaortitis/periarteritis based on the analysis of 179 patients with IgG4-related disease: a case-control study. *Arthritis Res Ther* 2017;19(1):223.

6 Wallace ZS, Zhang Y, Perugino CA, Naden R, Choi HK, Stone JH. Clinical phenotypes of IgG4-related disease: an analysis of two international cross-sectional cohorts. *Ann Rheum Dis* 2019;78(3):406-12.

7 Wang M, Zhang P, Lin W, et al. Differences and similarities between IgG4-related disease with and without dacryoadenitis and sialoadenitis: clinical manifestations and treatment efficacy. *Arthritis Res Ther* 2019;21(1):44.

8 Kamisawa T, Zen Y, Pillai S, Stone JH. IgG4-related disease. *Lancet* 2015;385(9976):1460-71.

9 Palmisano A, Urban ML, Corradi D, et al. Chronic periaortitis with thoracic aorta and epiaortic artery involvement: a systemic large vessel vasculitis? *Rheumatology* 2015;54(11):2004-9.

10 Perugino CA, Wallace ZS, Meyersohn N, Oliveira G, Stone JR, Stone JH. Large vessel involvement by IgG4-related disease. *Medicine* 2016;95(28):e3344.

11 Stone JR. Aortitis, periaortitis, and retroperitoneal fibrosis, as manifestations of IgG4-related systemic disease. *Curr Opin Rheumatol* 2011;23(1):88-94.

12 Castelein T, Coudyzer W, Blockmans D. IgG4-related periaortitis vs idiopathic periaortitis: is there a role for atherosclerotic plaque in the pathogenesis of IgG4-related periaortitis? *Rheumatology* 2015;54(7):1250-6.

13 Kim IY, Eun YH, Jeong H, et al. Clinical characteristics and outcomes of 61 patients with chronic periaortitis including IgG4-related and non-IgG4-related cases. *Int J Rheum Dis* 2017;20(11):1751-62.

14 Vaglio A, Catanoso MG, Spaggiari L, et al. Interleukin-6 as an inflammatory mediator and target of therapy in chronic periaortitis. *Arthritis Rheum* 2013;65(9):2469-75.

15 Umehara H, Okazaki K, Masaki Y, et al. Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. *Mod Rheumatol* 2012;22(1):21-30.

16 Umehara H, Okazaki K, Nakamura T, et al. Current approach to the diagnosis of IgG4-related disease - Combination of comprehensive diagnostic and organ-specific criteria. *Mod Rheumatol* 2017;27(3):381-91.

17 Schanzer A, Greenberg RK, Hevelone N, et al. Predictors of abdominal aortic aneurysm sac enlargement after endovascular repair. *Circulation* 2011;123(24):2848-55.

18 Caspary L. Inflammatory diseases of the aorta. *VASA* 2016;45(1):17-29.

19 Wallace ZS, Khosroshahi A, Carruthers MD, et al. An International Multispecialty Validation Study of the IgG4-Related Disease Responder Index. *Arthritis Care Res* 2018;70(11):1671-8.

20 Campochiaro C, Ramirez GA, Bozzolo EP, et al. IgG4-related disease in Italy: clinical features and outcomes of a large cohort of patients. *Scand J Rheumatol* 2016;45(2):135-45.

21 Yunyun F, Yu P, Panpan Z, et al. Efficacy and safety of low dose Mycophenolate mofetil treatment for immunoglobulin G4-related disease: a randomized clinical trial. *Rheumatology* 2019;58(1):52-60.

22 Brito-Zeron P, Ramos-Casals M, Bosch X, Stone JH. The clinical spectrum of IgG4-related disease. *Autoimmun Rev* 2014;13(12):1203-10.

23 Tomelleri A, Campochiaro C, Sartorelli S, et al. Gender differences in clinical presentation and vascular pattern in patients with Takayasu arteritis. *Scand J Rheumatol* 2019:1-9.

24 Yamamoto H, Sugiyama E, Serikawa M, et al. Clinical features and predictive value of serum inflammatory markers of perivascular involvement in immunoglobulin G4-related disease. *Heart vessels* 2017;32(10):1176-85.

25 Mizushima I, Inoue D, Yamamoto M, et al. Clinical course after corticosteroid therapy in IgG4-related aortitis/periaortitis and periarteritis: a retrospective multicenter study. *Arthritis Res Ther* 2014;16(4):R156.

26 Mizushima I, Kasashima S, Fujinaga Y, Kawano M, Ishizaka N. IgG4-related periaortitis/periarteritis: An under-recognized condition that is potentially life-threatening. *Mod Rheumatol* 2019;29(2):240-50.

27 Kasashima S, Kawashima A, Kasashima F, Endo M, Matsumoto Y, Kawakami K. Inflammatory features, including symptoms, increased serum interleukin-6, and C-reactive protein, in IgG4-related vascular diseases. *Heart vessels* 2018;33(12):1471-81.

28 Keser G, Aksu K, Direskeneli H. Discrepancies between vascular and systemic inflammation in large vessel vasculitis: an important problem revisited. *Rheumatology* 2018;57(5):784-90.

29 Wang L, Zhang P, Wang M, et al. Failure of remission induction by glucocorticoids alone or in combination with immunosuppressive agents in IgG4-related disease: a prospective study of 215 patients. *Arthritis Res Ther* 2018;20(1):65.

30 Wallace ZS, Mattoo H, Carruthers M, et al. Plasmablasts as a biomarker for IgG4-related disease, independent of serum IgG4 concentrations. *Ann Rheum Dis* 2015;74(1):190-5.

31 Lin W, Zhang P, Chen H, et al. Circulating plasmablasts/plasma cells: a potential biomarker for IgG4-related disease. *Arthritis Res Ther* 2017;19(1):25.

32 Culver EL, Sadler R, Bateman AC, et al. Increases in IgE, Eosinophils, and Mast Cells Can be Used in Diagnosis and to Predict Relapse of IgG4-Related Disease. *Clin Gastroenterol Hepatol* 2017;15(9):1444-52.e6.

33 Palmisano A, Maritati F, Vaglio A. Chronic Periaortitis: an Update. *Curr Rheumatol Rep* 2018;20(12):80.

34 Binder M, Uhl M, Wiech T, et al. Cyclophosphamide is a highly effective and safe induction therapy in chronic periaortitis: a long-term follow-up of 35 patients with chronic periaortitis. *Ann Rheum Dis* 2012;71(2):311-2.

35 Yunyun F, Yu C, Panpan Z, et al. Efficacy of Cyclophosphamide treatment for immunoglobulin G4-related disease with addition of glucocorticoids. *Sci Rep* 2017;7(1):6195.

36 Rossi GM, Rocco R, Accorsi Buttini E, Marvisi C, Vaglio A. Idiopathic retroperitoneal fibrosis and its overlap with IgG4-related disease. *Intern Emerg Med* 2017;12(3):287-99.

Tables

Table 1: Demographic features of IgG4-RD with/without PAO/PA

*represented statistical significance.

Demographic features	PAO/PA (n=89)	non-PAO/PA(n=498)	*P* value
Age (years)	58.3±11.1	52.6±13.8	<0.001*
Male/Female	5.85/1	1.35/1	<0.001*
Disease duration(month), M (Q_1-Q_3)	6 (2.5-36)	12 (6-36)	<0.001*
History of allergy (n, %)	25 (28.1)	267 (53.6)	<0.001*
IgG4-RD RI	10.8±5.3	9.8±5.2	0.103
Number of organs involved	2.9±1.9	3.0±1.7	0.126
Patients with single organ involved (n,%)	24 (27.0)	66 (13.3)	0.001*

Table 2: Onset symptoms and organs involvement of IgG4-RD patients with/without PAO/PA

Symptoms and organs affected at baseline	PAO/PA	non-PAO/PA	*P* value
Symptoms at disease onset (n, %)			
back pain	32 (36)	21 (4.2)	<0.001*
lymph node swelling	22 (24.7)	137 (27.5)	0.575
abdominal pain	25 (28.1)	79 (15.9)	0.005*
submandibular gland enlargement	18 (20.2)	213 (42.8)	<0.001*
lacrimal gland enlargement	10 (11.2)	227 (45.6)	<0.001*
Lower limb edema	14 (15.7)	8 (1.6)	<0.001*
cough	11 (12.4)	53 (10.6)	0.632
nausea and vomiting	12 (11.1)	42 (8.4)	0.129
jaundice	8 (9.0)	72 (14.5)	0.166
parotid gland enlargement	5 (5.6)	66 (13.3)	0.042*
nasal congestion	4 (4.5)	106 (21.3)	<0.001*
itching	5 (5.6)	45 (9.0)	0.287
Organs affected (n, %)			
lymph node	33 (37.1)	219 (44)	0.674
submandibular gland	24 (27.0)	259 (52)	<0.001*
pancreas	26 (29.2)	175 (35.5)	0.278
lung	15 (16.9)	117 (23.5)	0.167
lacrimal gland	11 (12.4)	266 (53.4)	<0.001*
parotid gland	9 (10.1)	90 (18.1)	0.065
bile duct	11 (12.4)	99 (19.9)	0.094
paranasal sinus	8 (9.0)	155 (31.1)	<0.001*
prostate	12 (15.8)	39 (13.6)	0.632
kidney	6 (6.7)	44 (8.8)	0.515
thyroid	2 (2.2)	21 (4.2)	0.378
pituitary	2 (2.2)	9 (1.8)	0.778
skin	1 (1.1)	28 (5.6)	0.071

Parameters	PAO/PA(n=89)	Non-PAO/PA(n=498)	*P* value
HgB (g/L)	127±21	135±19	<0.001*
WBC (10^9/L)	7.9±2.8	7.15±2.55	0.014*
PLT (10^9/L)	240±87	238±89	0.862
Eos% elevation(%)	22.5	32.4	0.077
ESR(mm/h), M (Q_1-Q_3)	44 (18-75)	16 (7-40)	<0.0001*
Elevation of ESR (n, %)	61 (77.1%, 61/70)	205 (42.0%, 205/488)	<0.001*
hsCRP(mg/L), M (Q_1-Q_3)	6.72 (2.14-24.65)	1.78 (0.72-5.12)	<0.0001*
Elevation of hsCRP (n, %)	56(70%, 56/80)	150 (37.5%, 150/400)	<0.001*
IgG (g/L)	19.88±8.20	21.28±14.46	0.292
IgA (g/L)	2.53±1.13	2.16±1.29	0.02*
IgM(g/L), M (Q_1-Q_3)	0.88 (0.56-1.14)	0.77 (0.54-1.19)	0.573
IgG1 (mg/L), M (Q_1-Q_3)	9355 (7928-11325)	8665 (7013-10600)	0.03
IgG2 (mg/L), M (Q_1-Q_3)	5705 (4255-7350)	5595 (4290-7520)	0.873
IgG3 (mg/L), M (Q_1-Q_3)	461 (221-923)	439 (253-841)	0.802
IgG4 (mg/L), M (Q_1-Q_3)	4240(2015-7730)	8310 (3250-17075)	<0.0001*
T-IgE (KU/L), M (Q1-Q3)	170 (95.3-463.5)	332 (119-720.5)	0.025*
Cr (μmol/L)	98.5 (73-131.3)	67 (57.7-78)	<0.0001*
Elevation of Cr (n, %)	38 (50)	14 (2.8)	<0.001*
C3 (g/L)	1.018±0.322	0.948±0.330	0.725
C4 (g/L)	0.217±0.112	0.173±0.102	0.004*

Table 3: Laboratory parameters of IgG4-RD patients with/without PAO/PA

M (Q1-Q3) represented median(Quartile1- Quartile3). *represented statistical significance.

Vessels affected (n, %)	Total (n=89)	Male (n=76)	Female (n=13)	*P* value
abdominal aorta	74 (83.1)	66 (86.8)	8 (61.5)	0.024*
iliac artery	63 (70.8)	57 (75.0)	6 (46.2)	0.035*
thoracic aorta	12 (13.5)	8 (10.5)	4 (30.8)	0.048*
other vessels	12(13.5)	7(9.2)	5(38.5)	0.004*
calcification of vessel wall	27 (30.3)	26 (34.2)	1 (7.7)	0.047*
diffuse thickening of the abdominal aortic wall	20 (22.5)	16 (21.1)	4 (30.8)	0.438
aneurysm	9 (10.1)	9 (11.8)	0 (0.0)	0.346
Type 1	5(5.6)	2(2.6)	3(23.1)	0.003*
Type 2	74(83.1)	66(86.8)	8(61.5)	0.024*
Type 3	7(7.9)	6(7.9)	1(7.7)	0.980
Type 4	3(3.4)	2(2.6)	1(7.7)	0.381

Table 4: Vascular distribution of IgG4-RD with PAO/PA

* represented statistical significance.

Figures

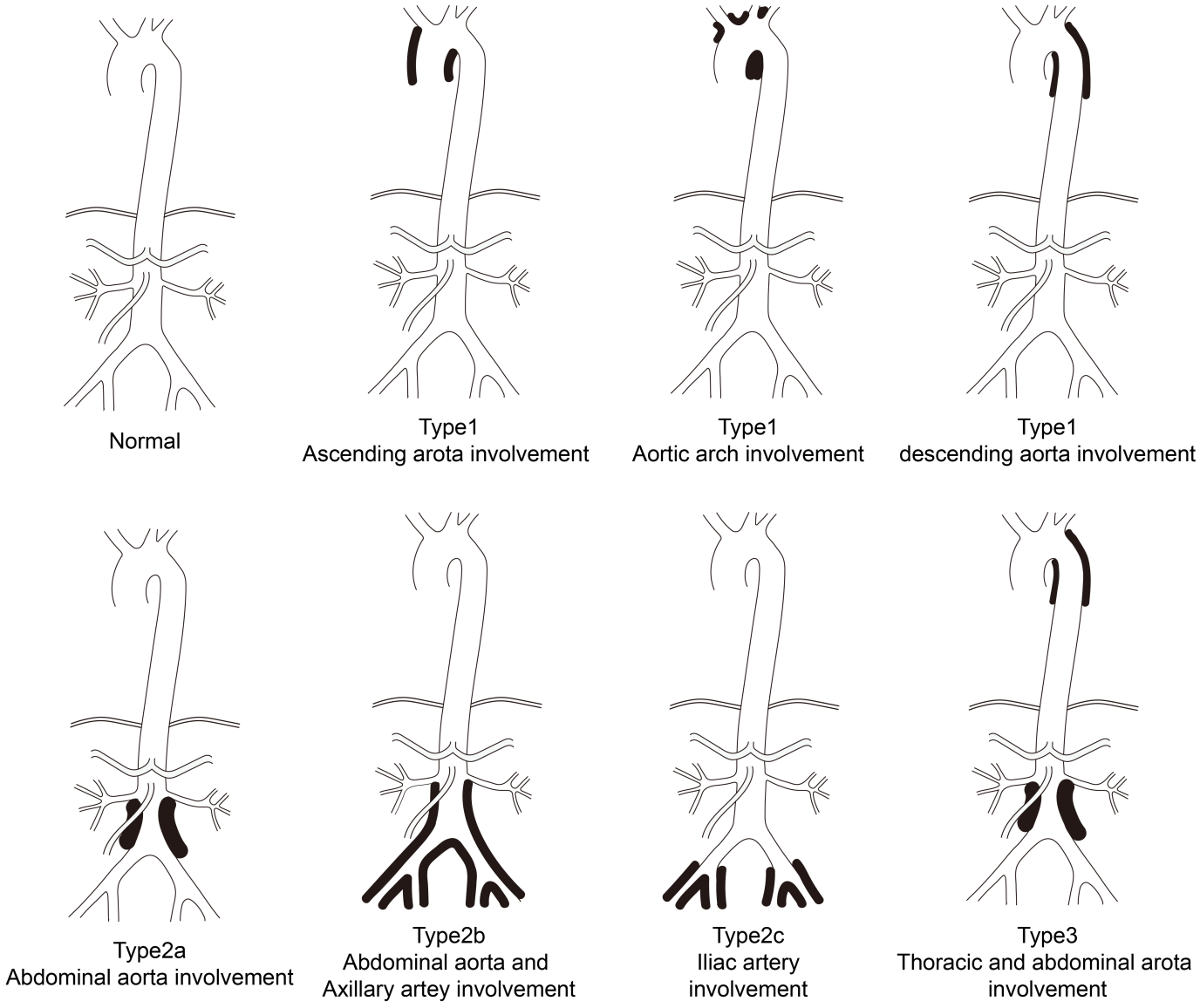

Figure 1

Classification of IgG4-related PAO/PA distribution.

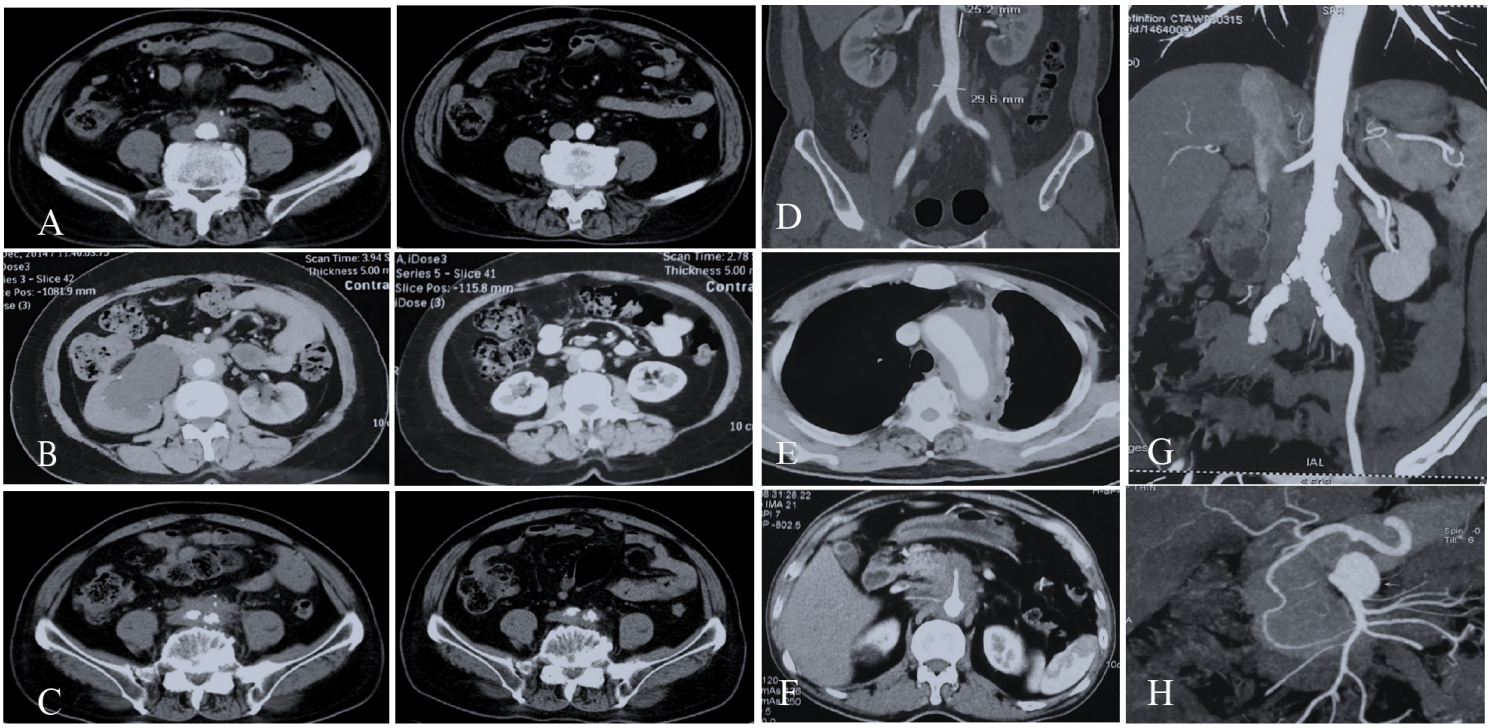

Figure 2

Characteristic imaging findings of IgG4-related PAO/PA Figure 2A: A 69-year-old man with periaortitis before and after treatment. Figure 2B: a 52-year-old woman with periaortitis and hydronephrosis before and after treatment. Figure 2C: Iliac artery affected before and after treatment of a 69-year-old man. Figure 2D and 2E: A 54-year-old man with thoracic aorta, abdominal, and iliac artery involvement. Figure 2F: Superior mesenteric artery involvement in a 64-year-old man. Figure 2G and 2H: Aneurysmal dilation of the abdominal aorta and superior mesenteric artery.