Vascular/perivascular inflammation in IgG4-related disease

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Abstract

Background. **Immunoglobulin G4-related disease (IgG4-RD) is characterized by the infiltration of IgG4-positive plasma cells and fibrosclerotic inflammation in multiple organs. Although vascular complications are present in some patients with IgG4-RD, vascular and/or perivascular inflammatory activity compared to control subjects remains unknown. This study sought to investigate vascular/perivascular inflammation by 18F-fluorodeoxyglucose-positron emission tomography combined with computed tomography (FDG-PET/CT) in IgG4-RD patients compared to control subjects.**

Methods. **We examined 37 consecutive patients diagnosed as IgG4-RD (29 males, mean age of 64.3±8.3 years old), who underwent FDG-PET/CT. Thirty-seven age- and gender-matched subjects without IgG4-RD were employed as controls. Vascular/perivascular inflammation was quantified by blood-normalized standardized uptake value, known as a target-to-background ratio (TBR).**

Results. **All IgG4-RD patients presented with multiple region involvements. Twelve (32.4%) of the IgG4-RD patients had vascular complications, all of which appeared in the abdominal aorta. IgG4-RD patients had significantly higher TBR values in the descending aorta, abdominal aorta, and common iliac arteries than control subjects. Also, IgG4-RD patients with vascular complications exhibited higher TBR values in the infra-renal aorta and common iliac artery than those without vascular complications.**

Conclusions. **We found that vascular FDG activity is significantly elevated in IgG4-RD patients regardless of vascular complications than control subjects. FDG-PET/CT is a useful modality for assessing vascular/perivascular inflammation, which may contribute vascular complications in IgG4-RD patients.**

Key Words: IgG4-related disease・vascular/perivascular inflammation・FDG-PET/CT・cardiovascular complication

Abbreviations

IgG4-RD	immunoglobulin G4-related disease
CT	computed tomography
MRI	magnetic resonance imaging
PET	positron emission tomography
FDG	18F-fluorodeoxyglucose
FPG	fasting plasma glucose
LDL	low-density lipoprotein
HDL	high-density lipoprotein
HbA_{1C}	glycated hemoglobin A_{1C}
eGFR	estimated glomerular filtration rate
CRP	C-reactive protein
IgG	immunoglobulin G
SUV	standardized uptake value
TBR	target-to-background ratio
CT(A)	CT angiography

BACKGROUND

Immunoglobulin G4-related disease (IgG4-RD) has been recognized as a systemic inflammatory disease, characterized by the infiltration of IgG4-positive plasma cells and fibrosclerotic change in multiple organs with the elevation of serum IgG4 levels.[1] Pancreas, biliary system, lacrimal and salivary glands, lymph node, lung, kidney, and retroperitoneum are potential targets for the disease involvement.[2] Also, IgG4-RD affects the cardiovascular system including aorta and branching medium-sized arteries.[3-7] Especially, aortic dissection, aortic aneurysm, and coronary artery involvement can be life-threatening conditions.[5-7] Cardiovascular complications of IgG4-RD are presumed to be associated with vascular and/or perivascular inflammation.[3,4] Computed tomography (CT) or magnetic resonance imaging (MRI) can depict signs suggestive of vascular inflammation in the arteries such as arterial wall thickening and homogeneous wall enhancement.[4,8,9] However, these conventional imaging modalities have ability to demonstrate structural features of cardiovascular complications, but not molecular information such as metabolic activity of inflammatory cells.

Inflammatory mechanism may include into the pathophysiology of IgG4-complicated cardiovascular system. However, it is hard to obtain vascular specimens in clinical settings. Cohort studies have reported the utility of positron emission tomography (PET) imaging with 18F-fluorodeoxyglucose (FDG) in IgG4-RD.[10,11] Furthermore, FDG-PET is a useful modality to monitor the therapeutic response in IgG4-RD.[11] Clinical studies have demonstrated that FDG-PET can directly estimate vascular inflammation in large vessel arteritis such as Takayasu arteritis and giant cell arteritis.[12] Therefore, FDG-PET may be employed to measure a surrogate marker of vascular/perivascular inflammation in IgG4-RD. Here, we perform comparative investigation for vascular/perivascular inflammation by FDG-PET in patients with IgG4-RD and control subjects without IgG4-RD.

METHODS

Patients and Study Design

Forty-two consecutive patients with suspected IgG4-RD were recruited for the candidate of this study. The diagnosis of IgG4-RD was based on the 2011 comprehensive diagnostic criteria for IgG4-RD proposed by Umehara et al.[13] Figure 1 presents a flow chart for the diagnosis of IgG4-RD. In brief, diagnostic criteria consist of (1) clinical examination showing characteristic diffuse/localized swelling or masses in single or multiple organs, (2) elevated serum IgG4 concentrations (≧135 mg/dL), and (3) infiltration of IgG4-positive plasma cells ($IgG4^+/IgG^+$ cell ratio >40% and >10 IgG4-positive plasma

cells/high power field). Patients who meet all 3 criteria have a definite diagnosis, and those who meet 2 criteria (1 and 2) with negative results on histopathology or without histopathologic examination are regarded as possible IgG4-RD. Even if serum levels of IgG4 were below 135 mg/dL, patients with histopathological features are deemed as probable IgG4-RD. The distribution of IgG4-RD lesions was assessed based on clinical characteristics and contrast-enhanced CT features in whole-body scans by 3 experienced physicians (T.U., Y.O., and H.K.).[13-18] In order to confirm the activity of IgG4-RD, FDG-PET combined with CT scan was performed separately from contrast-enhanced CT. These evaluations were carried out within two weeks. Age- and gender-matched subjects without IgG4-RD, who underwent FDG-PET/CT with dedicated vascular protocol to assess vascular inflammation for medical examinations of the cardiovascular system, were also recruited as controls. We excluded any patients with age < 20 years, acute infections, active inflammatory diseases, uncontrolled diabetes (fasting plasma glucose [FPG] ≥ 200 mg/dL), neoplastic disorders, and taking corticosteroid or immunosuppressant therapy prior to FDG-PET/CT scan. Patients who received insulin injections for the treatment of diabetes mellitus were also excluded. All participants gave informed consent to participate in this study. The Ethical Committee for the Clinical Research of Kurume University approved this study.

Data Collection

The medical history and smoking habit were ascertained by a questionnaire. Blood pressure was measured in the sitting position by the conventional cuff method using an upright mercury sphygmomanometer. Vigorous physical activity and smoking were avoided for at least 60 minutes before resting blood pressure and heart rate measurements. Fasting blood was drawn from the antecubital vein for determinations of complete blood count, liver chemistries (hepatocellular and cholestatic enzymes), lipid profiles {low-density lipoprotein (LDL) cholesterol, triglycerides, and high-density lipoprotein (HDL) cholesterol}, glycemic state [FPG, glycated hemoglobin (HbA_{1C})], uric acid, estimated glomerular filtration rate (eGFR), and inflammatory markers [C-reactive protein (CRP), erythrocyte sedimentation rate, immunoglobulin G (IgG), and IgG4]. These blood chemistry variables were measured by standard methods at a commercial laboratory (The Kyodo Igaku Laboratory, Fukuoka, Japan and SRL Inc., Tokyo, Japan) as described previously.[19] The value for HbA_{1C} (%) is estimated as a National Glycohemoglobin Standardization Program equivalent value (%) calculated by the formula; HbA_{1C} (National Glycohemoglobin Standardization Program) (%) = 1.02 × HbA_{1C} (Japan

Diabetes Society) (%) + 0.25%.[20] eGFR was calculated using the Modification of Diet in Renal Disease study equation modified with a Japanese coefficient.[21]

FDG-PET and CT

Vascular/perivascular inflammation was evaluated by FDG-PET combined with CT imaging using dedicated protocol for vascular inflammation as described previously.[22] In brief, after at least 12 hour-fasting prior to PET scanning, patients received an intravenous injection administration of FDG [4.2 MBq (0.12 mCi)/kg body weight] via the antecubital vein. In this study, 2 hours after the FDG injection, 3-dimensional PET and CT scans were carried out using an integrated full-ring PET/CT scanner (Gemini-GXL 16; Philips Medical Systems, Inc., Cleveland, Ohio, USA). The CT data were used for attenuation correction and lesion localization. After both the transmission and emission images were obtained, the images were reconstructed using the 3D line-of-response row-action maximum likelihood algorithm (3D-LOR-RAMLA; Philips, Eindhoven, The Netherlands). The co-registration of PET and CT imaging was performed for review on a workstation (Sun Microsystems, Inc., Santa Clara, California). The intensity of FDG uptake was quantified by measuring the standardized uptake value (SUV) corrected for body weight. The SUV was calculated by using the maximum pixel activity value within the region of interest placed on the vascular wall of the transaxial PET/CT image. Arterial SUV scores were determined as the average of the SUVs obtained from 5 consecutive PET/CT images in each separated region by 4 mm in length (Figure 2) and then were adjusted for each subject's FPG level to account for a competitive impact of glucose and FDG using an established formula as follows: $SUV_{glucose} = SUV \times FPG / 90$ mg/dL.[23,24] Subsequently, the $SUV_{glucose}$ scores were corrected for blood pool activity by dividing the average blood SUV scores estimated from the inferior vena cava (Figure 2), known as target-to-background ratio (TBR).[22-24] These procedures were performed by two investigators experienced in PET/CT studies (S.I. and M.B.). The intra-observer or inter-observer variability of TBR values was less than 5%.

Image Analysis

FDG uptake of the arteries were measured at the following 6 regions; first 3 branches from the thoracic aorta, ascending aorta, descending aorta, supra-renal abdominal aorta, infra-renal abdominal aorta, and bilateral common iliac arteries (Figure 2) FDG-PET scans at the abdominal portion were acquired in all patients with IgG4-RD and control subjects without IgG4-RD. There were several incomplete scans of other portions in IgG4-RD patients (Figure 3). The luminal diameters > 45 mm at the thoracic aorta and >

30 mm at the abdominal aorta were defined as aortic aneurysm according to the Japanese Circulation Society 2011 guidelines for diagnosis and treatment of aortic aneurysm and aortic dissection.[25] The maximum wall thickness was measured on axial images of contrast-enhanced CT. Diffuse arterial wall thickening ≥ 2 mm, homogeneous enhancement on contrast-enhanced CT, and development of aneurysm or dissection were considered as vascular complications in IgG4-RD as previously describe.[26]

Statistics

Continuous variables were presented as mean values ± standard deviation or medians with the interquartile range. Categorical variables were described in numbers and percentages. We performed the Shapiro-Wilk test to evaluate the assumption of normality. Statistical analyses were performed by means of appropriate parametric and nonparametric methods. Continues variables between two groups were compared using Student's t-test. The χ^2 test was used for categorical parameters to test differences between groups. Values of less than 0.05 were considered to be statistically significant. All statistical analyses were performed with the use of the SPSS system (IBM, Chicago, IL, USA).

RESULTS

Diagnosis of IgG4-related Disease

Thirty-two of 42 patients showed abnormal increases in serum IgG4 levels exceeding 135 mg/dL (Figure 1). The 32 patients underwent biopsy or surgery, in which 15 (46.9%) exhibited IgG4-positive plasma cell infiltration. Histopathological features diagnosed 5 patients as "probable" IgG4-RD and 5 patients as non IgG4-RD, if serum levels of IgG4 were below 135 mg/dL. The study patients were classified into definite (n=15), possible (n=17), probable (n=5) and excluded (n=5) IgG4-RD categories. The 22 patients with "possible" or "probable" IgG4-RD had been diagnosed with autoimmune pancreatitis based on the International Consensus Diagnostic Criteria 2011.[17] Therefore, they were regarded as IgG4-RD in this study. Finally, thirty-seven patients (29 males, mean age of 64.3 ± 8.3 years old) were measured vascular FDG activity.

Patient Characteristics

Characteristics of the IgG4-RD patients and control subjects without IgG4-RD are presented in Table 1. There were no significant differences in body mass index, heart rate, blood pressure, lipid profiles, estimated glomerular filtration rate, and smoking habits rate between the 2 groups. Despite of being within the normal limits, hepatocellular and

cholestatic enzymes such as aspartate transaminase, alanine transaminase, alkaline phosphatase, and γ-glutamyl transpeptidase levels in IgG4-RD patients were significantly higher than those in control subjects. Serum levels of amylase were similar in both groups. Glycemic state was impaired in IgG4-RD patients. Inflammatory markers including white blood cells, CRP, and IgG were elevated in IgG4-RD patients. The prevalence of hypertension, dyslipidemia, and diabetes was comparable among the 2 groups.

Table 2 demonstrates characteristics of the IgG4-RD patients with and without vascular complications. Elderly or male predominance was not observed in IgG4-RD patients with vascular complications. The prevalence of cerebral vascular disease and serum levels of uric acid, IgG, IgG4, and CRP in IgG4-RD patients with vascular complications were significantly higher than those without vascular complications.

Distribution and Inflammatory Activity in IgG4-related Disease

As shown in Figure 4, all IgG4-RD patients showed multiple region involvements such as submandibular gland swelling (n=10, 27.0%), pulmonary lesions (n=13, 35.1%), hilar lymph adenopathy (n=24, 64.9%), pancreatitis (n=32, 86.5%), and retroperitoneal fibrosis (n=12, 32.4%). Vascular complications presenting with periaortitis/periarteritis, FDG-avid hypermetabolic thickened wall and/or aortic aneurysm were seen in 12 patients (32.4%) of IgG4-RD, all of which affected in the abdominal aorta. There was no IgG4-RD patient with aortic dissection or coronary involvement in our study. In the assessments of FDG activity within the 6 vascular regions (Figure 2), IgG4-RD patients had higher TBR values in the descending aorta, supra-renal and infra-renal abdominal aortas, and common iliac arteries compared to control subjects (Table 3). There were no significant differences in TBR values within the ascending aorta and the first 3 branches from thoracic aorta among them. IgG4-RD patients with vascular complications presented with higher TBR values in the infra-renal aorta and common iliac arteries than those without vascular complications (Table 4). Figures 5 and 6 demonstrate representative cases with IgG4-related vascular complications. FDG-PET/CT and contrast-enhanced CT images demonstrate FDG-avid hypermetabolic thickened wall and spotty calcification from infra-renal abdominal aorta to right common iliac artery (Figure 5). Two- and three-dimensional CT with contrast media indicate an infra-renal abdominal aortic aneurysm (Figure 6). Fused FDG-PET and CT images demonstrate an FDG-avid hypermetabolic aortic wall of the abdominal aortic aneurysm (Figure 6). Since the aortic aneurysm was rapidly growing to 5.5 cm in its maximum diameter, the patient underwent a surgically aortic repair. The gross finding showed a ceramic-like aortic aneurysm (Figure 7). The aneurysm was repaired through the use of a standard graft inclusion technique with

collagen-coated Dacron tube grafts. Unfortunately, ureteral injury was occurred as a complication due to tight adhesion to surrounding structures of the abdominal aorta. Immunopathological analyses confirmed IgG4-positive cell infiltration in the aortic wall samples (Figure 7).

DISCUSSION

In the present study, we systematically assessed vascular/perivascular inflammation in 37 patients with IgG4-RD and compared with 37 control subjects. The key findings of our study were that [1] all IgG4-RD patients showed multiple region involvements, most of the patients showed IgG4-related lesions in the retroperitoneal organs, [2] approximately 30% of the IgG4-RD patients presented with vascular complications such as FDG-avid hypermetabolic thickened wall and/or aortic aneurysm, [3] IgG4-RD patients had significantly higher TBR values in the descending aorta, abdominal aorta, and common iliac arteries compared to control subjects, and [4] IgG4-RD patients with vascular complications presented with higher TBR values within infra-renal aorta and common iliac artery than those without vascular complications.

IgG4-RD is known as a sclerosing disease, which was first recognized in the setting of autoimmune pancreatitis with high serum IgG4 concentration in 2001.[1] Thereafter, it has become known that many other organs can also have similar IgG4-related pathology.[27] Typically, large numbers of IgG4-positive plasma cells are present in the tissue obtained from biopsy specimens.[28] In the present study, 20 cases (62.5%) presented IgG4-positive plasma cells. Measurement and clinical significance of serum IgG4 has dramatically increased in the past 20 years due to the emergence of IgG4-RD.[29] Although serum IgG4 concentrations in IgG4-RD patients were generally high, 30% of the patients have within normal limits.[30] In our study, even with serum IgG4 levels below 135 mg/dL, 5 patients (13.5%) were diagnosed as IgG4-RD based on the presence of autoimmune pancreatitis and immunohistopathological findings.

Several reports have demonstrated IgG4-RD in various cardiovascular complications.[31-36] Umehara et al. pointed out periaortitis/periarteritis and inflammatory aortic aneurysm as two types of vascular complications in IgG4-RD.[13] Vascular complications such as periaortitis/periarteritis or aortic aneurysm were seen in approximately 30-40% patients with IgG4-RD.[33,34,36] In our study, the prevalence of vascular complications (12/37 patients, 32.4%) was similar with the previous reports.[33,34,36] As shown in Table 4, there were significant differences of TBR values within infra-renal abdominal aorta and common iliac artery between IgG4-RD patients with and without vascular complications. IgG4-related vascular complications are often

observed in the aorta, its branches, and coronary arteries.[2] Above all, the vascular complications predominantly affect in the infra-renal abdominal aorta and iliac arteries.[4,26,35,36] Chronic shear stress to the arteries may be one of the reasons leading morphological changes.[37] Also, IgG4-related vascular complications might be associated with atherosclerotic changes,[3] since atherosclerotic lesions are frequently observed in the infra-renal abdominal aorta and iliac arteries. However, the distribution of IgG4-related vascular complications is clearly different between Caucasian and Japanese patients.[35,38] Although ethnicity could affect the disparity, clear clarifications are limited in the present study. Vascular FDG uptake may demonstrate inflammatory activity in the complex complications with atherosclerosis and IgG4-related vascular lesions. However, our purpose was to investigate the vascular FDG activity in patients with IgG4-RD compared to control subjects, but not to distinguish between IgG4-RD and atherosclerosis. In our study, differences in vascular FDG activity between the control and IgG4-RD groups were relatively low (Table 3), when we compared with a previous study, in which the FDG activity was measured over the volume of interest placed over the hot lesions.[10] The reasons of the differences in vascular FDG activity could be the different selection site of vascular beds and measuring method. Autoimmune pancreatitis and retroperitoneal fibrosis are included in IgG4-RD, which is characterized by numerous infiltrating IgG4-positive plasma cells and high serum IgG4 concentration.[13] In this study, there were frequent IgG4-RD lesions in the pancreas and retroperitoneum, and all vascular complications were seen in the infra-renal abdominal aorta. Blood pressure, heart rate, lipid profile except for triglycerides, or comorbidities in IgG4-RD patients were similar with those in age- and gender-matched control subjects. There were significant differences in the clinical and laboratory parameters involving in IgG4-RD. Therefore, autoimmune pancreatitis and/or retroperitoneal fibrosis could be an inflammatory pathogenesis of IgG4-related vascular complications.

Recently, utility of the whole-body FDG-PET/CT angiography (CTA) scan for diagnosis of IgG4-RD has been reported, especially in systemic organs.[8,10,12,39] In prospective cohort study of IgG4-RD patients, CTA can demonstrate morphologic changes in the vessels and FDG-PET can reveal inflammatory complications in multi-organs more than conventional modalities.[10,39] FDG-PET has excellent sensitivity for detection of IgG4-RD lesions, which are correlated with inflammatory activity.[10,11] Also, FDG-PET has been employed for detecting vascular inflammation.[9,21,40] In the present study, we measured TBR values by FDG-PET/CT for evaluation of vascular inflammation, because the TBR value is a quantitative parameter of inflammatory cell activity with highly reliability.[17,41] Indeed, there was a significant correlation between CRP levels and

TBR values within the infra-renal abdominal aorta (r= 0.366, P= 0.026). Additionally, we obtained the PET imaging 2 hours after the FDG injection because delayed phase image could allow sufficient FDG accumulation in the arterial wall and to permit blood levels of FDG to become more reduced by decay and washout compared with the image obtained 1 hour after FDG administration, which is commonly used for oncologic PET.[18,41] Since inflammation plays an essential role in the development and progression of cardiovascular disease,[43,44] IgG4-RD patients with vascular inflammatory activity and no vascular complication could develop vascular lesions in the future. Although IgG4-related aneurysm is characterized by thickened aortic wall, retroperitoneal fibrosis, and tight adhesion to surrounding structures, some cases with ruptured aortic aneurysm have been reported.[6,40] Therefore, early diagnosis of vascular involvement, especially inflammatory activity, is a crucial for patients with IgG4-RD. In this study, we focused on the vascular inflammation in patients with IgG4-RD and evaluated the quantitative assessment of FDG activity in the aorta and branching medium-sized arteries. Compared to control subjects, IgG4-RD patients without vascular complications had higher TBR values in the infra-renal abdominal aorta (1.69 ± 0.36 vs 1.96 ± 0.62, P= 0.035) and common iliac arteries (1.24 ± 0.26 vs 1.45 ± 0.30, P= 0.026). Vascular complications might develop before structural change in patients with IgG4-RD. The confirmation of inflammatory activity could substantially contribute to therapeutic approaches for inhibition of vascular complications. Hence, FDG-PET may be useful for detecting in the early stage of IgG4-RD with vascular involvements.

Significant limitations should be considered in the present study. First, this is a single-center study. Single-center data limits the sample size and the generalizability of our findings by its selection bias. For instance, elderly or male predominance was not observed in IgG4-RD patients with vascular complications in this study, which is inconsistent with other studies.[26,34] Also, FDG-PET scans were performed as clinically indicated in patients with IgG4-RD, which could yield its selection bias. The selection bias may limit and confound the present findings. Second, we could not confirm other pathophysiological conditions causing vascular complications in all IgG4-RD patients due to our inability in obtaining significant $IgG4^+$ plasma cells. Misdiagnosis of IgG4-RD could be occurred without histological evidence. Meeting international consensus diagnostic criteria[45] would enhance the robustness of our cohort. Third, there were significant differences in FPG levels between IgG4-RD patients and control subjects in this study. FDG uptake into inflammatory cells could be competitively inhibited by

glucose. Previous studies have shown that intensity of FDG uptake in inflammatory tissues is influenced by individual glucose levels.[46,47] Therefore, we adjusted the FDG uptake in the aorta and its branches for each subject's FPG levels according to the European Association of Nuclear Medicine recommendations on PET imaging.[23] Fourth, this study was cross-sectional and thus could not assess the questions of whether IgG4-RD patients with vascular inflammatory activity develop and progress vascular lesions in the future. IgG4-RD patients with contrast-enhanced CT features indicated FDG-avid hypermetabolic thickened wall and elevated CRP levels in our study, thereby which might be associated with the probability of vascular complications. Future longitudinal studies are needed to confirm the issue. Fifth, there were several missing portions of FDG-PET scans in the IgG4-RD group. The absence of statistical significance in the 3 branches from the ascending aorta and ascending aorta was likely caused by the missing data, although descending aorta was significant despite missing data due to much stronger effect. Sixth, FDG-PET/CT scan was collected at a single point. Follow-up FDG-PET/CT scan is required to identify structural and inflammatory changes of vascular complications especially in patients with corticosteroid therapy.

CONCLUSIONS

We assessed the vascular inflammation by FDG-PET/CT in patients with IgG4-RD compared to control subjects without IgG4-RD. We found that vascular FDG activity is significantly elevated in IgG4-RD patients regardless of vascular complications than control subjects. FDG-PET/CT is a useful modality for assessing vascular/perivascular inflammation, which may contribute vascular complications in IgG4-RD patients.

NEW KNOWLEDGE GAINED

Vascular/perivascular inflammation that may lead to altered vascular properties is significantly elevated in IgG4-RD patients regardless of vascular complications than control subjects. Future studies are needed to validate whether IgG4-RD patients with vascular inflammatory activity develop and progress vascular lesions.

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Disclosure

All authors have nothing to disclose regarding the current study.

References

1) Hamano H, Kawa S, Horiuchi A, Unno H, Furuya N, Akamatsu T, et al. High serum IgG4 concentrations in patients with sclerosing pancreatitis. N Engl J Med 2001;344:732-8.
2) Stone JH, Khosroshahi A, Deshpande V, Chan JK, Heathcote JG, Aalberse R, et al. Recommendations for the nomenclature of IgG4-related disease and its individual organ system manifestations. Arthritis Rheum 2012;64:3061-7.
3) Tajima M, Nagai R, Hiroi Y. IgG4-related cardiovascular disorders. Int Heart J 2014;55:287-95.
4) Inoue D, Zen Y, Abo H, Gabata T, Demachi H, Yoshikawa J, et al. Immunoglobulin G4-related periaortitis and periarteritis: CT findings in 17 patients. Radiology 2011;261:625-33.
5) Uchida T, Hamasaki A, Kuroda Y, Sadahiro M, Tamazawa N, Ohe R, et al. Immunoglobulin G Subclass 4-Related Lymphoplasmacytic Thoracic Aortitis in a Patient with Acute Type A Aortic Dissection. Ann Thorac Cardiovasc Surg 2018;24:208-10.
6) Qian Q, Kashani KB, Miller DV. Ruptured abdominal aortic aneurysm related to IgG4 periaortitis. N Engl J Med 2009;361:1121-3.
7) Patel NR, Anzalone ML, Buja LM, Elghetany MT. Sudden cardiac death due to coronary artery involvement by IgG4-related disease: a rare, serious complication of a rare disease. Arch Pathol Lab Med 2014;138:833-6.
8) Horger M, Lamprecht HG, Bares R, Spira D, Schmalzing M, Claussen CD, et al. Systemic IgG4-related sclerosing disease: spectrum of imaging findings and differential diagnosis. AJR Am J Roentgenol 2012;199:W276-82.
9) Mavrogeni S, Markousis-Mavrogenis G, Kolovou G. IgG4-related cardiovascular disease. The emerging role of cardiovascular imaging. Eur J Radiol 2017;86:169-75.
10) Zhang J, Chen H, Ma Y, Xiao Y, Niu N, Lin W, et al. Characterizing IgG4-related disease with ^{18}F-FDG PET/CT: a prospective cohort study. Eur J Nucl Med Mol Imaging 2014;41:1624-34.
11) Nakatani K, Nakamoto Y, Togashi K. Utility of FDG PET/CT in IgG4-related systemic disease. Clin Radiol 2012;67:297-305.
12) Soussan M, Nicolas P, Schramm C, Katsahian S, Pop G, Fain O, et al. Management of large-vessel vasculitis with FDG-PET: a systematic literature review and meta-analysis. Medicine (Baltimore) 2015;94:e622.

13) Umehara H, Okazaki K, Masaki Y, Kawano M, Yamamoto M, Saeki T, et al. Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. Mod Rheumatol 2012;22:21-30.
14) Masaki Y, Sugai S, Umehara H. IgG4-related diseases including Mikulicz's disease and sclerosing pancreatitis: diagnostic insights. J Rheumatol 2010;37:1380-5.
15) Matsui S. IgG4-related respiratory disease. Mod Rheumatol 2019;29:251-6.
16) Okazaki K, Kawa S, Kamisawa T, Naruse S, Tanaka S, Nishimori I, et al; Research Committee of Intractable Diseases of the Pancreas. Clinical diagnostic criteria of autoimmune pancreatitis: revised proposal. J Gastroenterol 2006;41:626-31.
17) Shimosegawa T, Chari ST, Frulloni L, Kamisawa T, Kawa S, Mino-Kenudson M, et al; International Association of Pancreatology. International consensus diagnostic criteria for autoimmune pancreatitis: guidelines of the International Association of Pancreatology. Pancreas 2011;40:352-8.
18) Kawano M, Saeki T, Nakashima H, Nishi S, Yamaguchi Y, Hisano S, et al. Proposal for diagnostic criteria for IgG4-related kidney disease. Clin Exp Nephrol 2011;15:615-26.
19) Tahara N, Yamagishi SI, Bekki M, Kodama N, Nakamura T, Sugiyama Y, et al. Anagliptin, A Dipeptidyl Peptidase-4 Inhibitor Ameliorates Arterial Stiffness in Association with Reduction of Remnant-Like Particle Cholesterol and Alanine Transaminase Levels in Type 2 Diabetic Patients. Curr Vasc Pharmacol 2016;14:552-62.
20) Hoelzel W, Weykamp C, Jeppsson JO, Miedema K, Barr JR, Goodall I, et al; IFCC Working Group on HbA1c Standardization. IFCC reference system for measurement of hemoglobin A1c in human blood and the national standardization schemes in the United States, Japan, and Sweden: a method-comparison study. Clin Chem 2004;50:166-74.
21) Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, et al. Revised equations for estimated GFR from serum creatinine in Japan. Am J Kidney Dis 2009;53:982-92.
22) Honda A, Tahara N, Nitta Y, Tahara A, Igata S, Bekki M, et al. Vascular Inflammation Evaluated by [18F]-Fluorodeoxyglucose-Positron Emission Tomography/Computed Tomography Is Associated With Endothelial Dysfunction. Arterioscler Thromb Vasc Biol 2016;36:1980-8.
23) Bucerius J, Hyafil F, Verberne HJ, Slart RH, Lindner O, Sciagra R, et al; Cardiovascular Committee of the European Association of Nuclear Medicine (EANM). Position paper of the Cardiovascular Committee of the European

Association of Nuclear Medicine (EANM) on PET imaging of atherosclerosis. Eur J Nucl Med Mol Imaging 2016;43:780-92.
24) Tahara N, Nitta Y, Bekki M, Tahara A, Maeda-Ogata S, Sugiyama Y, et al. Two-hour postload plasma glucose and pigment epithelium-derived factor levels are markers of coronary artery inflammation in type 2 diabetic patients. J Nucl Cardiol 2020;27:1352-64.
25) JCS Joint Working Group. Guidelines for diagnosis and treatment of aortic aneurysm and aortic dissection (JCS 2011): digest version. Circ J 2013;77:789-828.
26) Yabusaki S, Oyama-Manabe N, Manabe O, Hirata K, Kato F, Miyamoto N, et al. Characteristics of immunoglobulin G4-related aortitis/periaortitis and periarteritis on fluorodeoxyglucose positron emission tomography/computed tomography co-registered with contrast-enhanced computed tomography. EJNMMI Res 2017;7:20.
27) Kawa S, Okazaki K, Kamisawa T, Shimosegawa T, Tanaka M. Japanese consensus guidelines for management of autoimmune pancreatitis: II. Extrapancreatic lesions, differential diagnosis. J Gastroenterol 2010;45:355-69.
28) Zen Y. Pathological characteristics and diagnosis of IgG4-related disease. Press Med 2020;49:104014.
29) Varghese JL, Fung AWS, Mattman A, Quach TTT, Gauiran DTV, Garruthers MN, et al. Clinical utility of serum IgG4 measurement. Clinica Chimica Acta 2020;506:228-35.
30) Sah RP, Chari ST. Serologic issues in IgG4-related systemic disease and autoimmune pancreatitis. Curr Opin Rheumatol 2011;23:108-13.
31) Kasashima S, Zen Y, Kawashima A, Konishi K, Sasaki H, Endo M, et al. Inflammatory Abdominal Aortic Aneurysm: Close Relationship to IgG4-related Periaortitis. Am J Surg Pathol 2008;32:197-204.
32) Agaimy A, Weyand M, Strecker T. Inflammatory thoracic aortic aneurysm (lymphoplasmacytic thoracic aortitis): a 13-year-experience at a German Heart Center with emphasis on possible role of IgG4. Int J Clin Exp Pathol 2013;6:1713-22.
33) Hourai R, Kasashima S, Sohmiya K, Yamauchi Y, Ozawa H, Hirose Y, et al. IgG4-positive cell infiltration in various cardiovascular disorders - results from histopathological analysis of surgical samples. BMC Cardiovascular Disorders 2017;17:52.
34) Perugino CA, Wallace ZS, Meyersohn N, Oliveira G, Stone JR, Stone JH. Large vessel involvement by IgG4-rerated disease. Medicine (Baltimore) 2016;95:e3344.

35) Mizushima I, Inoue D, Yamamoto M, Yamada K, Saeki T, Ubara Y, et al. Clinical course after corticosteroid therapy in IgG4-related aortitis/periaortitis and periarteritis:a retrospective multicenter study. Arthritis Res Ther 2014;16:156.
36) Ozawa M, Fujinaga Y, Asano J, Nakamura A, Watanabe T, Ito T, 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;19:223.
37) Sughimoto K, Shimamura Y, Tezuka C, Tsubota K, Liu H, Okumura K, et al. Effects of arterial blood flow on walls of the abdominal aorta: distributions of wall shear stress and oscillatory shear index determined by phase-contrast magnetic resonance imaging. Heart Vessels 2016;31:1168–75.
38) 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;54:1250-6.
39) Pelletier-Galarneau M, Ruddy TD. PET/CT for Diagnosis and Management of Large-Vessel Vasculitis. Curr Cardiol Rep 2019;21:34.
40) Kasashima S, Zen Y, Kasashima A, Endo M, Matsumoto Y, Kasashima F. A new clinicopathological entity of IgG4-related inflammatory abdominal aortic aneurysm. J Vasc Surg 2009;49:1264-71.
41) Rudd JH, Myers KS, Bansilal S, Machac J, Pinto CA, Tong C, et al. Atherosclerosis Inflammation Imaging with 18F-FDG PET: Carotid, Iliac, and Femoral Uptake Reproducibility, Quantification Methods, and Recommendations. J Nucl Med 2008;49:871-8.
42) Bucerius J, Mani V, Moncrieff C, Machac J, Fuster V, Farkouh ME, et al. Optimizing 18F-FDG PET/CT imaging of vessel wall inflammation: the impact of 18F-FDG circulation time, injected dose, uptake parameters, and fasting blood glucose levels. Eur J Nucl Med Mol Imaging. 2014;41:369-83.
43) García-Martínez A, Hernández-Rodríguez J, Arguis P, Paredes P, Segarra M, Lozano E, et al. Development of Aortic Aneurysm/Dilatation During the Follow up of Patients With Giant Cell Arteritis: A Cross-Sectional Screening of Fifty-Four Prospectively Followed Patients. Arthritis Rheum 2008;59:422-30.
44) Muratore F, Crescentini F, Spaggiari L, Pazzola G, Casali M, Boiardi L, et al. Aortic dilatation in patients with large vessel vasculitis: A longitudinal case control study using PET/CT. Semin Arthritis Rheum 2019;48:1074-82.
45) Wallace ZS, Naden RP, Chari S, Choi H, Della-Torre E, Dicaire JF, et al; American College of Rheumatology/European League Against Rheumatism IgG4-Related Disease Classification Criteria Working Group. The 2019 American College of

Rheumatology/European League Against Rheumatism classification criteria for IgG4-related disease. Arthritis Rheumatol 2020;72:7-19.
46) Zhuang HM, Cortés-Blanco A, Pourdehnad M, Adam LE, Yamamoto AJ, et al. Do high glucose levels have differential effect on FDG uptake in inflammatory and malignant disorders? Nucl Med Commun 2001;22:1123-8.
47) Rabkin Z, Israel O, Keidar Z. Do hyperglycemia and diabetes affect the incidence of false-negative 18F-FDG PET/CT studies in patients evaluated for infection or inflammation and cancer? A Comparative analysis. J Nucl Med 2010;51:1015-20.

Figure legend

Figure 1. A flow chart for the diagnosis of IgG4-RD

A flow chart showing the diagnosis of IgG4-RD. Thirty-seven of 42 patients were diagnosed as IgG4-RD. The study patients were classified into definite (n=15), possible (n=17), probable (n=5) and excluded (n=5) IgG4-RD categories.

Figure 2. Imaging analysis of vascular beds

Arterial and venous SUV scores were determined as the average of the SUVs obtained from 5 consecutive PET/CT images in each separated region by 4 mm in length.

Figure 3. Number of IgG4-RD patients for assessment of FDG activity in six vascular regions

FDG-PET scans at the abdominal portion were acquired in all patients with IgG4-RD and all control subjects without IgG4-RD. There were several incomplete scans of other portions in IgG4-RD patients.

Figure 4. Whole body distribution of IgG4-related lesions

Whole body distribution of IgG4-related lesions. All IgG4-RD patients showed multiple region involvements such as submandibular gland swelling, pulmonary lesions, hilar lymph adenopathy, pancreatitis, and retroperitoneal fibrosis.

Head and neck: Symmetrical swelling of at least 2 pairs of the lacrimal, parotid, or submandibular glands continuing for more than 3 months. Differential diagnosis is necessary from other disorders, including sarcoidosis, Castleman's disease, Wegener's granuloma, and cancer.

Chest: Abnormal shadow on chest CT: a. Hilar/mediastinal lymphadenopathy, b. Thickening of bronchial wall, bronchovascular bundle, interlobular septal wall, c. Nodular shadow, infiltrative shadow, pleural thickening/effusion.

Abdomen: Diffuse or segmental narrowing of the main pancreatic duct with irregular wall (more than 1/3 length of the entire pancreas) and diffuse or localized enlargement of the pancreas by imaging studies. It is necessary to exclude malignant diseases such as

pancreatic and biliary cancers.

Abnormal renal radiologic findings: a. Multiple low-density lesions on enhanced computed tomography b. Diffuse kidney enlargement c. Hypovascular solitary mass in the kidney d. Hypertrophic lesion of renal pelvic wall without irregularity of the renal pelvic surface. Clinically and histologically, the following disease should be excluded: Wegener's granulomatosis, Churg-Strauss syndrome, extramedullary plasmacytoma.

Radiologically, the following disease should be excluded: malignant lymphoma, urinary tract carcinomas, renal infarction, and pyelonephritis (rarely, Wegener's granulomatosis, sarcoidosis and metastatic carcinoma).

Figure 5. A representative case with IgG4-related vascular complication

IgG4-related vascular complication in a 73-year-old woman. FDG-PET/CT and 2-D/3-D contrast-enhanced CT (CECT) images demonstrating FDG-avid hypermetabolic thickened wall and spotty calcification from infra-renal abdominal aorta to right common iliac artery.

Figure 6. A representative case with IgG4-related vascular complication

IgG4-related vascular complication in a 71-year-old man. FDG-PET/CT and 2-D/3-D contrast-enhanced CT (CECT) images demonstrating infra-renal abdominal aortic aneurysm with indicative active inflammation. The aneurysm wall shows irregular thickness with calcification.

Figure 7. Gross and microscopic findings of vascular complication in IgG4-RD

Gross finding showing a ceramic-like infra-renal aortic aneurysm. Histological sections from the abdominal aorta reveals the adventitia is markedly thickened due to inflammatory cell infiltration accompanied by fibrous proliferation. Dense lymphoplasmacytic infiltration with fibrosis is observed. Immunohistochemistry for IgG and IgG4 demonstrating IgG4-positive plasma cells are more than 40% of the IgG-positive cells. There are more than 10 IgG4-positive plasma cells per high power field (HPF).

Table 1. Characteristics of control subjects and IgG4-RD patients

Parameters	Control	IgG4-RD	P value
Number	37	37	
Age, years	63.6 ± 10.0	64.3 ± 8.3	0.746
Male gender, n (%)	27 (73.0)	29 (78.4)	0.588
Past smoking†, n (%)	19 (51.4)	23 (62.2)	0.348
Body mass index, kg/m^2	22.5 ± 2.6	21.7 ± 3.2	0.263
Heart rate, beats/minute	67.7 ± 11.1	70.8 ± 10.5	0.234
Systolic blood pressure, mmHg	120.8 ± 12.3	119.7 ± 15.6	0.733
Diastolic blood pressure, mmHg	74.2 ± 9.1	73.5 ± 11.1	0.761
Aspartate transaminase*, IU/L	22.0 (19.0-25.0)	24.0 (18.0-55.0)	**0.018**
Alanine transaminase*, IU/L	20.0 (16.0-24.0)	22.0 (15.0-57.0)	**0.013**
Alkaline phosphatase*, IU/L	195.0 (176.0-224.0)	295.0 (218.0-434.0)	**<0.001**
γ-glutamyl transpeptidase*, IU/L	27.0 (21.0-40.0)	37.0 (21.0-204.0)	**0.007**
Total bilirubin*, mg/dL	0.87 (0.69-1.04)	0.70 (0.53-1.26)	0.580
Amylase*, IU/L	74.5 (65.8-85.8)	60.0 (48.0-97.3)	0.725
LDL cholesterol, mg/dL	125.4 ± 24.8	110.7 ± 37.2	0.083
Triglycerides*, mg/dL	86.0 (74.0-143.0)	101.5 (81.5-168.8)	**0.001**
HDL cholesterol, mg/dL	57.1 ± 11.4	57.7 ± 19.1	0.882
Fasting plasma glucose*, mg/dL	108.0 (101.0-112.0)	120.0 (111.0-137.0)	**0.001**
Glycated hemoglobin, %	5.47 ± 0.50	6.36 ± 1.57	**0.002**
Estimated glomerular filtration rate, mL/min	69.4 ± 14.0	79.1 ± 27.5	0.064
Uric acid, mg/dL	6.28 ± 1.46	4.94 ± 1.41	**<0.001**
White blood cells*, /μL	5100 (4500-6300)	6800 (5700-7900)	**<0.001**
Red blood cells, $\times 10^4/\mu L$	457.4 ± 41.6	436.7 ± 63.3	0.105
Hemoglobin, g/dL	14.2 ± 1.3	13.1 ± 2.0	**0.004**
Hematocrit, %	42.0 ± 3.9	39.0 ± 5.9	**0.014**
Platelet, $\times 10^4//\mu L$	19.7 ± 5.4	23.5 ± 9.4	**0.042**
C-reactive protein*, mg/dL	0.04 (0.04-0.08)	0.13 (0.04-0.73)	**<0.001**
Erythrocyte sedimentation rate*, mm/hr	7.5 (7.3-7.8)	27.0 (17.0-82.0)	0.167
Immunoglobulin G*, mg/dL	1136.5 (1066.8-1284)	1775.0 (1502.5-2312.5)	**<0.001**

Immunoglobulin G4*, mg/dL	25.5 (18.7-44.7)	331.0 (182.0-939.0)	**<0.001**
Hypertension†, n (%)	14 (37.8)	13 (35.1)	0.809
Dyslipidemia†, n (%)	6 (16.2)	9 (24.3)	0.386
Diabetes mellitus†, n (%)	5 (13.5)	10 (27.0)	0.148
Coronary artery disease†, n (%)	0 (0)	3 (8.1)	0.077
Cerebral vascular disease†, n (%)	0 (0)	3 (8.1)	0.077

Values are mean ± standard deviation or *median (interquartile range). † No=0, Yes=1. n=number. Bold values indicate the statistically significant values.

Table 2. Characteristics of IgG4-RD patients with and without vascular complications

Parameters	IgG4-RD without vascular complications	IgG4-RD with vascular complications	P value
Number	25	12	
Age, years	63.2 ± 8.8	66.6 ± 6.5	0.257
Male gender, n (%)	19 (76.0)	10 (83.3)	0.606
Past smoking†, n (%)	16 (64.0)	7 (58.3)	0.740
Body mass index, kg/m^2	22.2 ± 3.1	19.4 ± 2.4	**0.011**
Heart rate, beats/minute	68.8 ± 8.6	74.9 ± 12.6	0.102
Systolic blood pressure, mmHg	117.3 ± 14.1	124.7 ± 17.4	0.190
Diastolic blood pressure, mmHg	72.4 ± 9.2	75.8 ± 13.9	0.403
Aspartate transaminase*, IU/L	22.0 (17.0-55.0)	24.5 (21.8-45.5)	0.853
Alanine transaminase*, IU/L	18.0 (13.0-34.0)	27.0 (17.8-64.0)	0.699
Alkaline phosphatase*, IU/L	283.0 (203.0-401.0)	308.0 (237.5.0-633.3)	0.659
γ-glutamyl transpeptidase*, IU/L	34.0 (20.0-204.0)	67.0 (30.3-183.8)	0.687
Total bilirubin*, mg/dL	0.80 (0.57-1.68)	0.57 (0.45-0.77)	0.158
Amylase*, IU/L	59.0 (49.5-92.3)	69.0 (44.3-107.0)	0.389
LDL cholesterol, mg/dL	111.6 ± 34.5	109.2 ± 41.3	0.891
Triglycerides*, mg/dL	101.5 (82.3-139.5)	110.5 (79.8-177.3)	0.458
HDL cholesterol, mg/dL	60.3 ± 18.6	53.5 ± 19.0	0.424
Fasting plasma glucose*, mg/dL	114.0 (110.0-126.0)	125.5 (119.5-140.0)	0.113
Glycated hemoglobin, %	6.08 ± 0.89	6.90 ± 2.32	0.150
Estimated glomerular filtration rate, mL/min	82.2 ± 26.3	72.6 ± 28.9	0.330
Uric acid, mg/dL	4.60 ± 1.07	5.66 ± 1.73	**0.033**
White blood cells*, /μL	6600 (5300-7300)	7450 (6750-8275)	0.120
Red blood cells, ×10^4/μL	444.3 ± 62.1	420.9 ± 63.0	0.305
Hemoglobin, g/dL	13.5 ± 1.6	12.3 ± 2.4	0.074
Hematocrit, %	40.2 ± 5.2	36.7 ± 6.8	0.097
Platelet, ×10^4/μL	23.5 ± 9.3	23.5 ± 9.8	0.986
C-reactive protein, mg/dL	0.10 (0.04-0.34)	0.19 (0.13-2.67)	**0.020**

Erythrocyte sedimentation rate, mm/hr	21.0 (17.0-26.5)	75.0 (41.0-85.0)	0.239
Immunoglobulin G, mg/dL	1745.0 (1394.5-2063.5)	2184.0 (1676.3-3371.0)	**0.021**
Immunoglobulin G4, mg/dL	369.0 (147.0-819.0)	286.0 (205.8-1635.0)	0.411
Hypertension†, n (%)	9 (36.0)	4 (33.3)	0.873
Dyslipidemia†, n (%)	6 (24.0)	3 (25.0)	0.947
Diabetes mellitus†, n (%)	4 (16.0)	6 (50.0)	**0.033**
Coronary artery disease†, n (%)	2 (8.0)	1 (8.3)	0.972
Cerebral vascular disease†, n (%)	0 (0)	3 (25.0)	**0.007**

Values are mean ± standard deviation or *median (interquartile range). † No=0, Yes=1. n=number. Bold values indicate the statistically significant values.

Table 3. TBR values of control subjects and IgG4-RD patients

Aortic regions	Control	IgG4-RD	P value
Three branches from the thoracic aorta	1.52 ± 0.38 (n=37)	1.74 ± 0.49 (n=13)	0.107
Ascending aorta	1.93 ± 0.43 (n=37)	2.11 ± 0.48 (n=15)	0.202
Descending aorta	1.95 ± 0.46 (n=37)	2.46 ± 0.79 (n=15)	**0.006**
Supra-renal abdominal aorta	1.70 ± 0.36 (n=37)	1.95 ± 0.48 (n=37)	**0.014**
Infra-renal abdominal aorta	1.69 ± 0.36 (n=37)	2.14 ± 0.75 (n=37)	**0.002**
Common iliac artery	1.24 ± 0.26 (n=22)	1.77 ± 0.89 (n=29)	**0.010**

Bold values indicate the statistically significant values.

Table 4. TBR values of IgG4-RD patients with and without vascular complication

Aortic regions	IgG4-RD without vascular complication	IgG4-RD with vascular complication	P value
Three branches from the thoracic aorta	1.82 ± 0.44 (N=9)	1.56 ± 0.56 (N=4)	0.420
Ascending aorta	2.22 ± 0.47 (N=10)	1.88 ± 0.42 (N=5)	0.224
Descending aorta	2.62 ± 0.84 (N=10)	2.14 ± 0.55 (N=5)	0.297
Supra-renal abdominal aorta	1.90 ± 0.47 (N=25)	2.07 ± 0.48 (N=12)	0.325
Infra-renal abdominal aorta	1.96 ± 0.62 (N=25)	2.50 ± 0.85 (N=12)	**0.040**
Common iliac artery	1.45 ± 0.30 (N=18)	2.32 ± 1.26 (N=11)	**0.012**

Bold values indicate the statistically significant values.

Figure 1

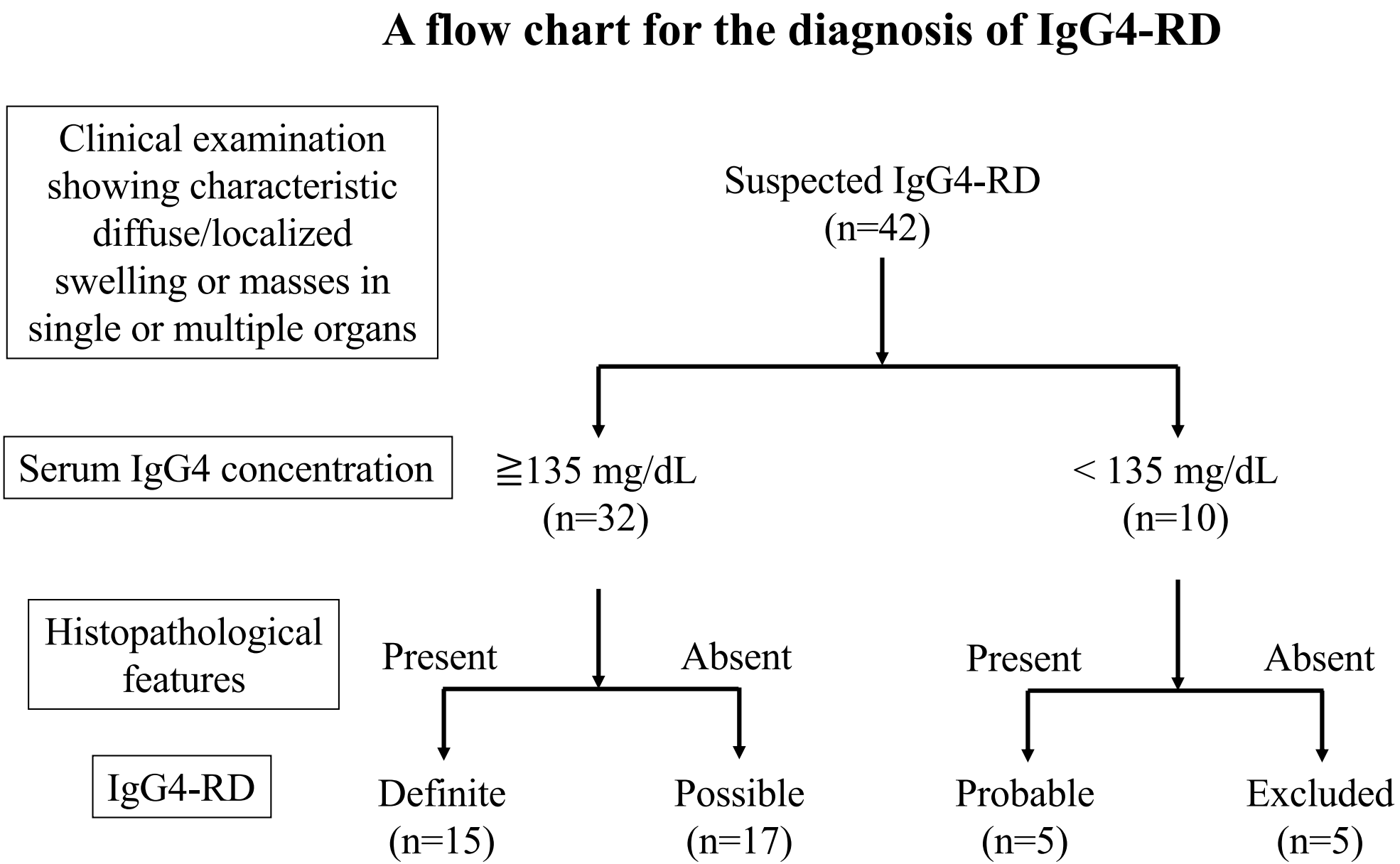

A flow chart for the diagnosis of IgG4-RD
Clinical examination showing characteristic diffuse/localized swelling or masses in single or multiple organs
Suspected IgG4-RD (n=42)
Serum IgG4 concentration
≧135 mg/dL (n=32)
< 135 mg/dL (n=10)
Histopathological features
Present
Absent
Present
Absent
IgG4-RD
Definite (n=15)
Possible (n=17)
Probable (n=5)
Excluded (n=5)

Figure 2

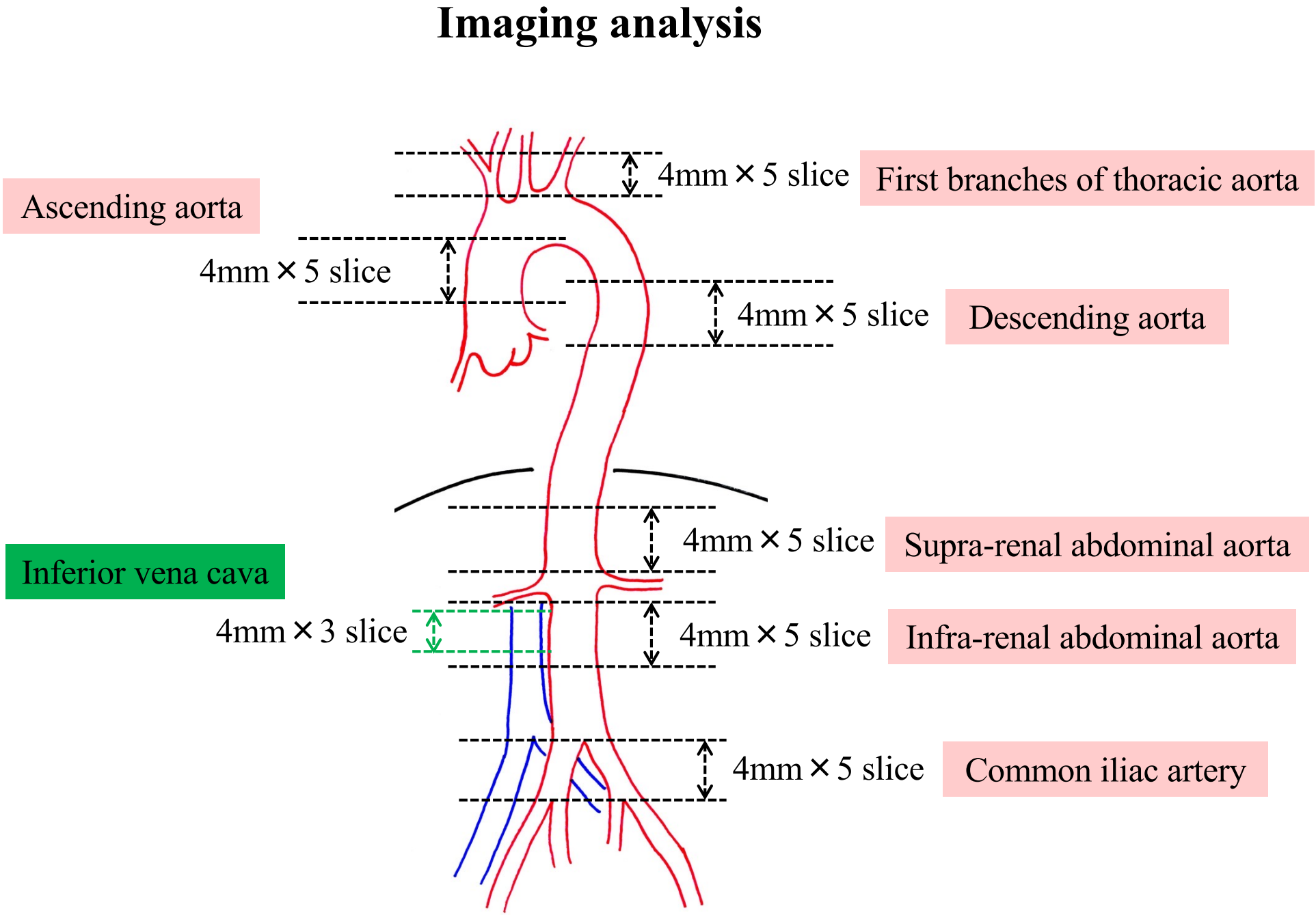

Imaging analysis
Ascending aorta
4mm × 5 slice
First branches of thoracic aorta
4mm × 5 slice
4mm × 5 slice
Descending aorta
Inferior vena cava
4mm × 5 slice
Supra-renal abdominal aorta
4mm × 3 slice
4mm × 5 slice
Infra-renal abdominal aorta
4mm × 5 slice
Common iliac artery

Figure 3

Number of IgG4-RD patients for assessment of FDG activity in six vascular regions

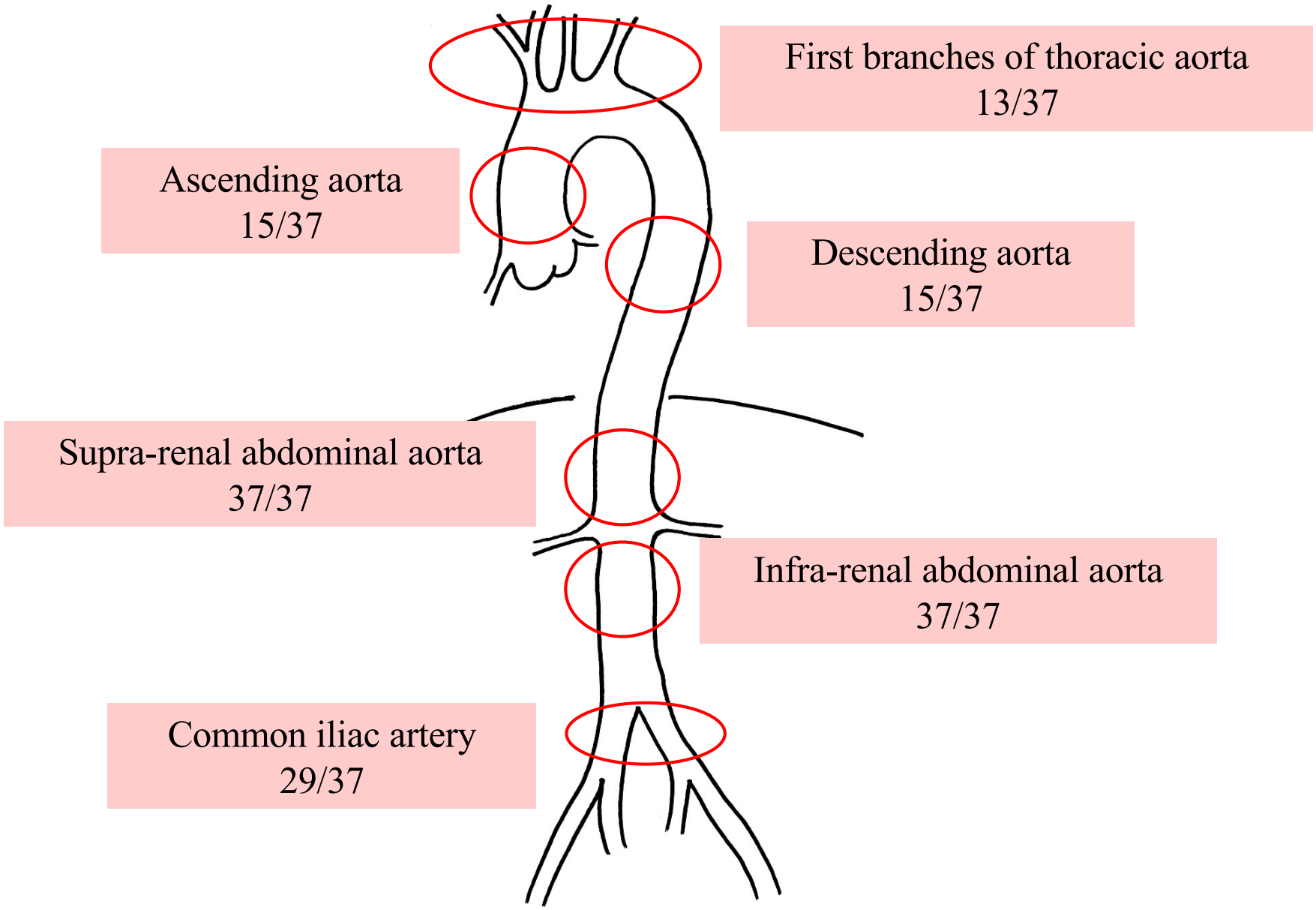


Figure 4

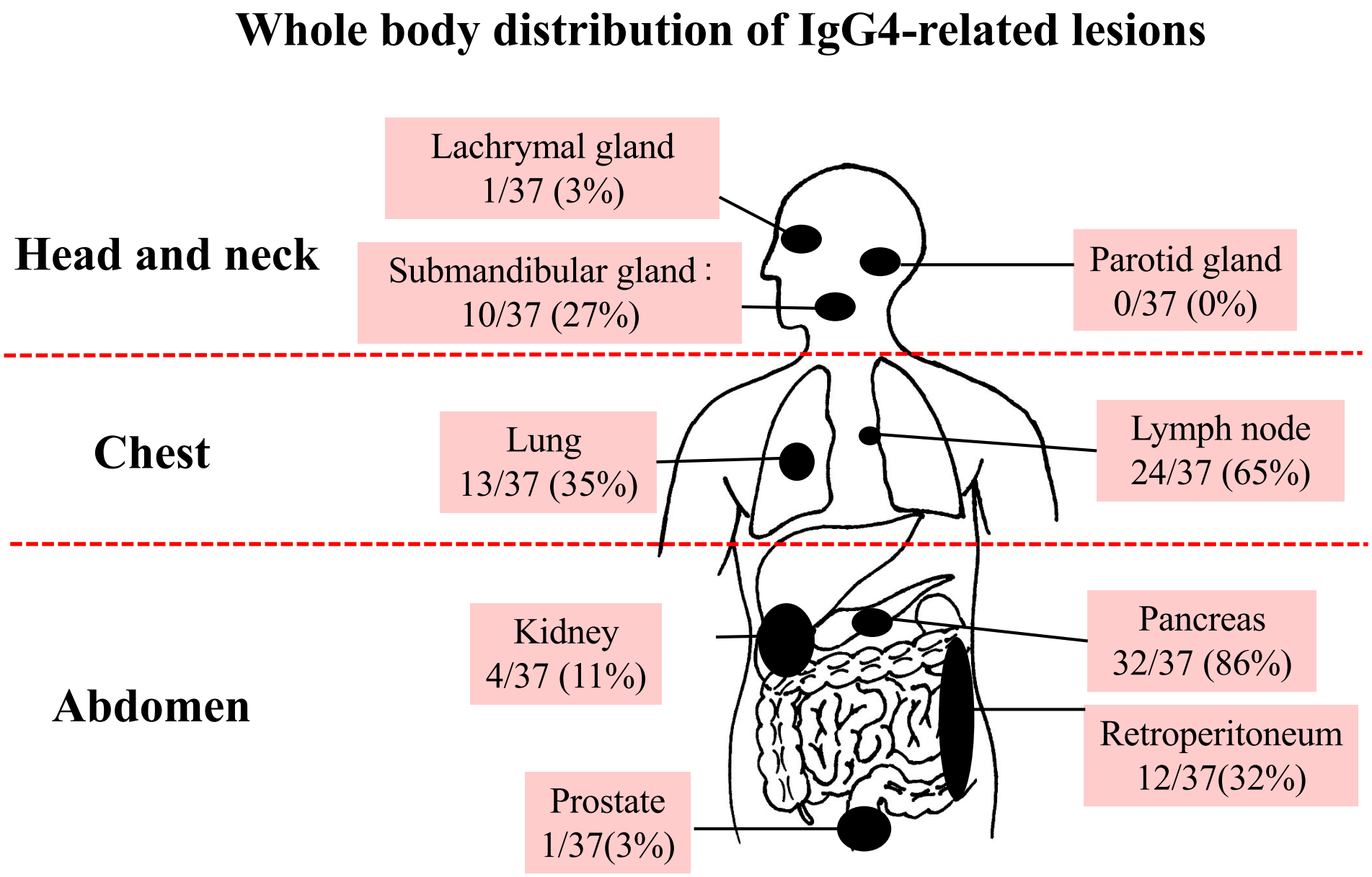

Whole body distribution of IgG4-related lesions
Head and neck
Chest
Abdomen
Lachrymal gland
1/37 (3%)
Submandibular gland :
10/37 (27%)
Parotid gland
0/37 (0%)
Lung
13/37 (35%)
Lymph node
24/37 (65%)
Kidney
4/37 (11%)
Pancreas
32/37 (86%)
Retroperitoneum
12/37(32%)
Prostate
1/37(3%)

Figure 5 A representative case with IgG4-related vascular complication

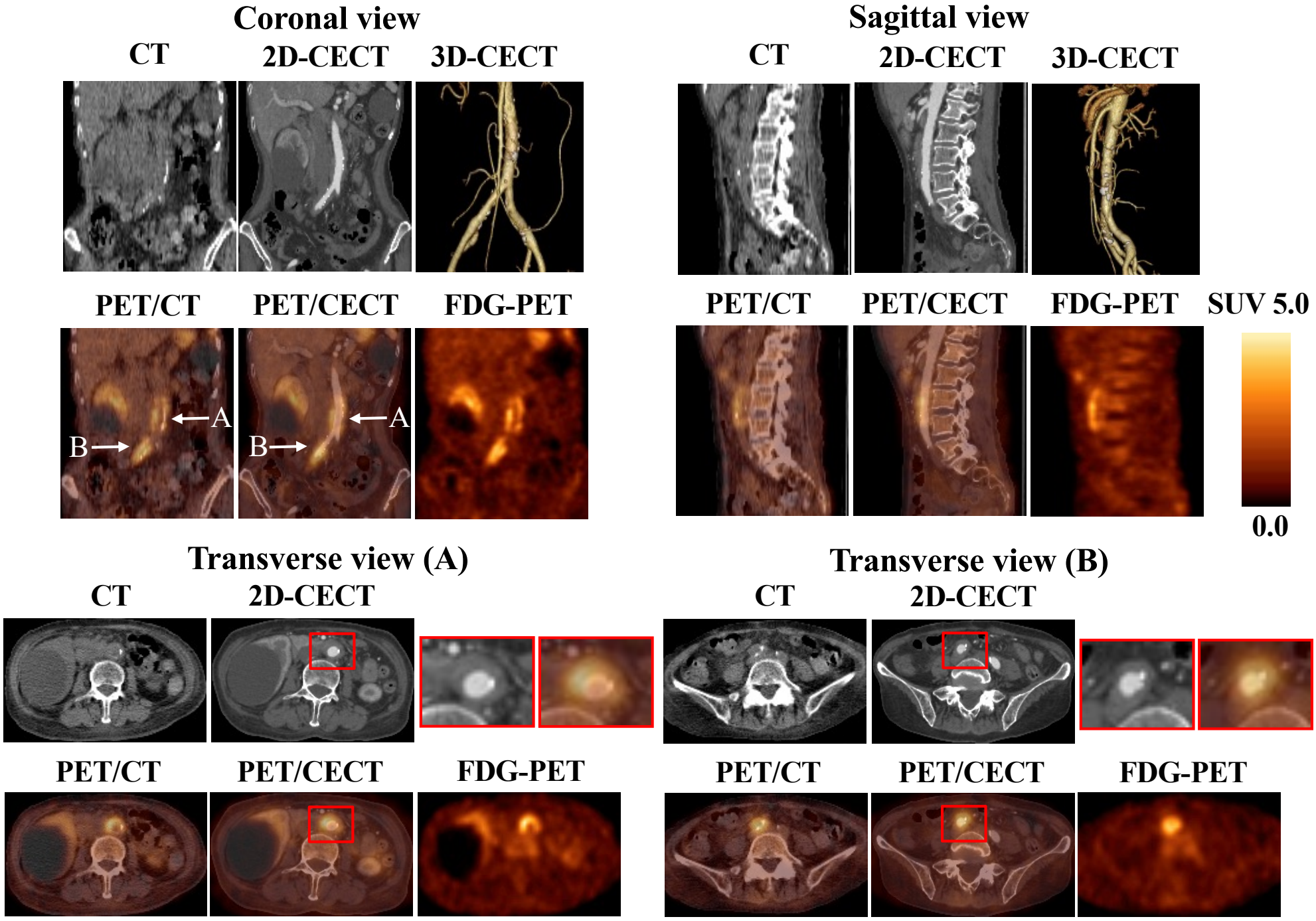


Figure 6

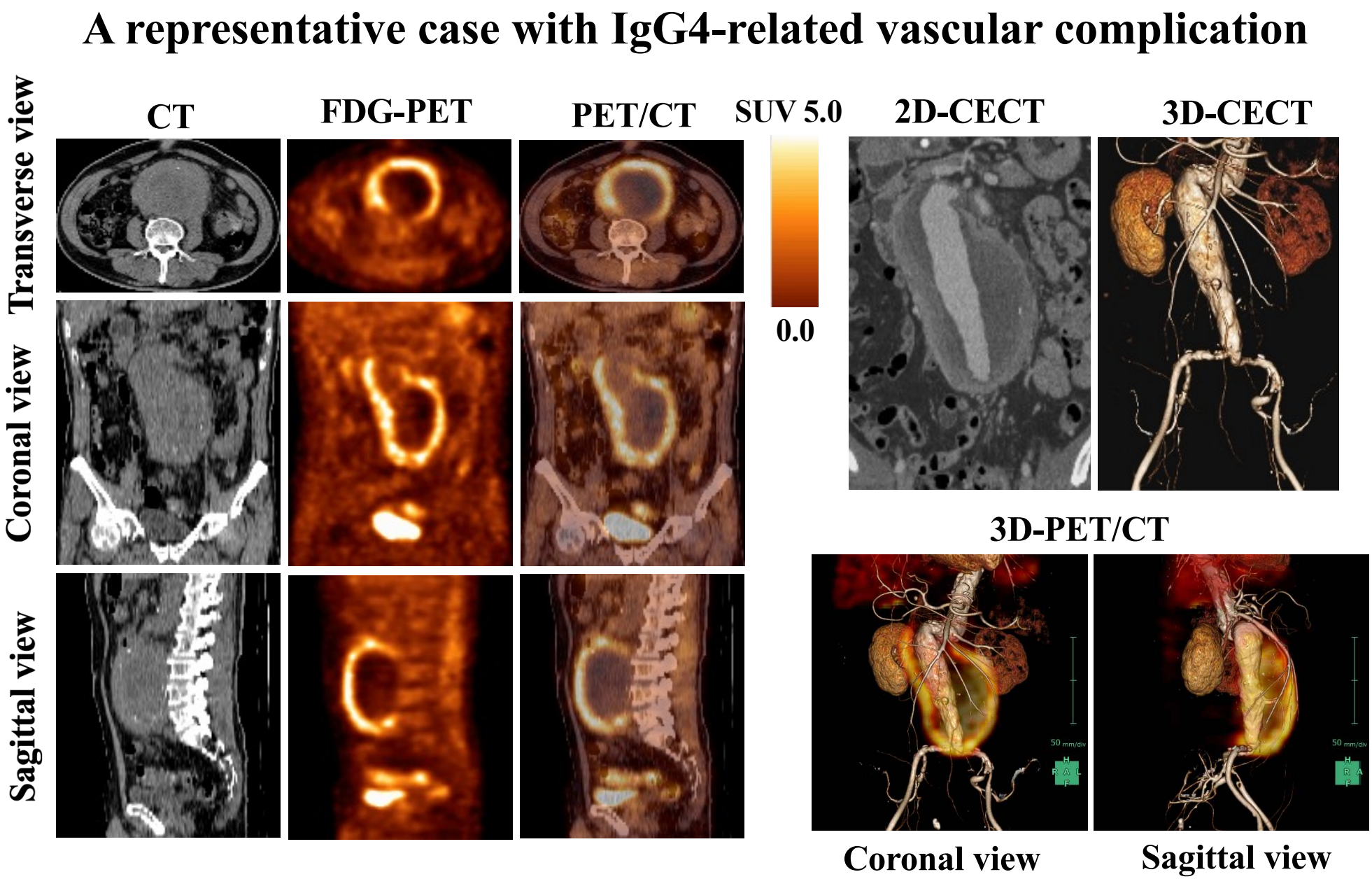
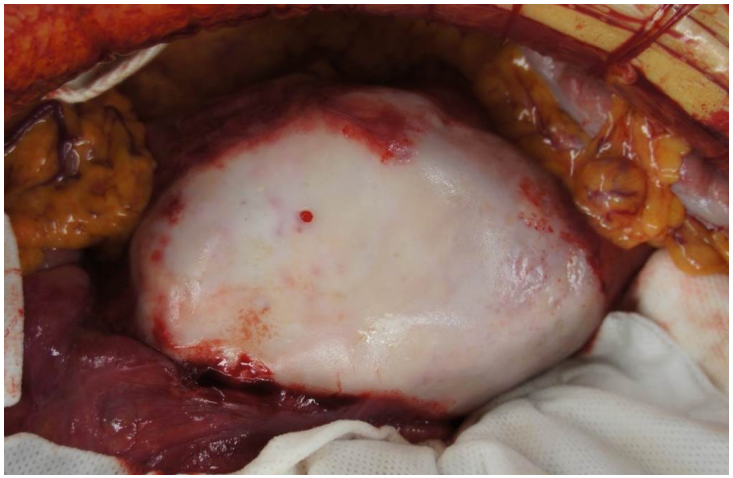
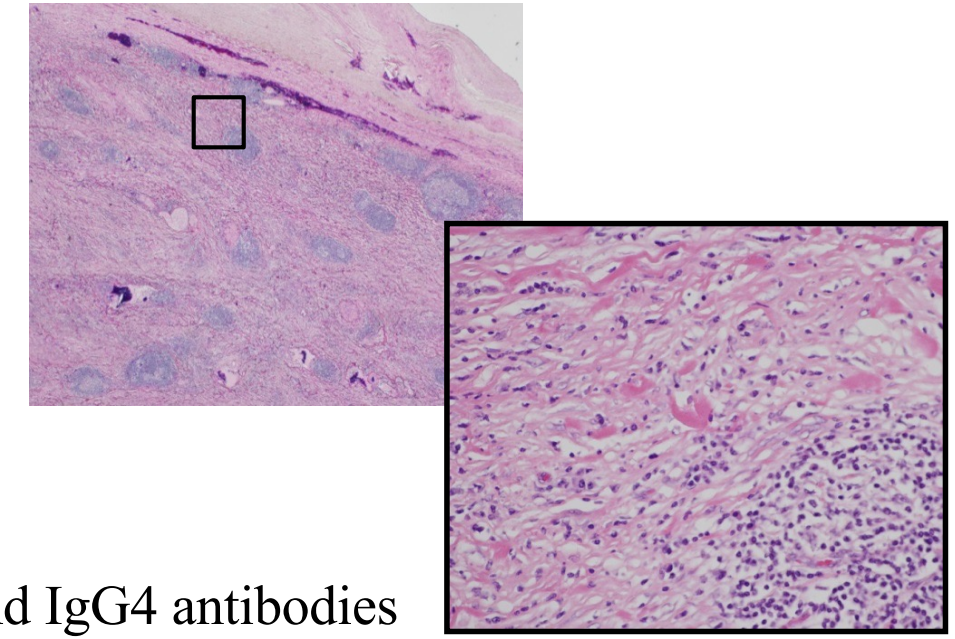

A representative case with IgG4-related vascular complication
CT
FDG-PET
PET/CT
SUV 5.0
0.0
2D-CECT
3D-CECT
Transverse view
Coronal view
Sagittal view
3D-PET/CT
Coronal view
Sagittal view

Figure 7

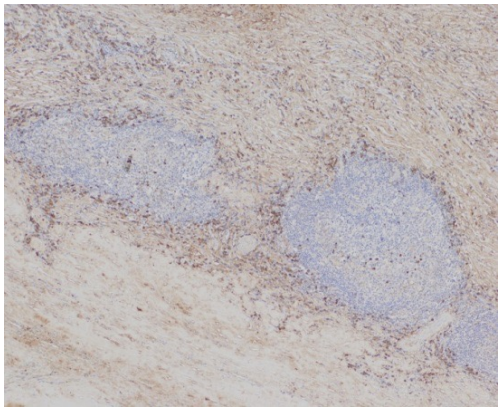
Gross and microscopic findings of vascular complication in IgG4-RD



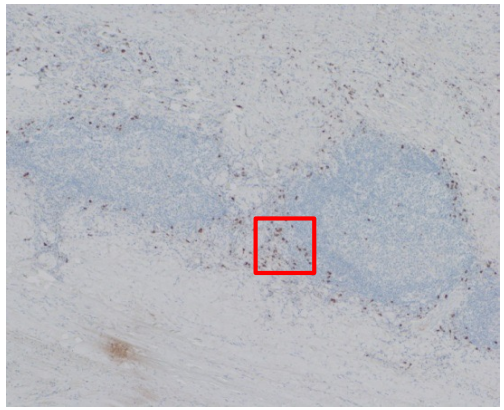
Hematoxylin and eosin staining



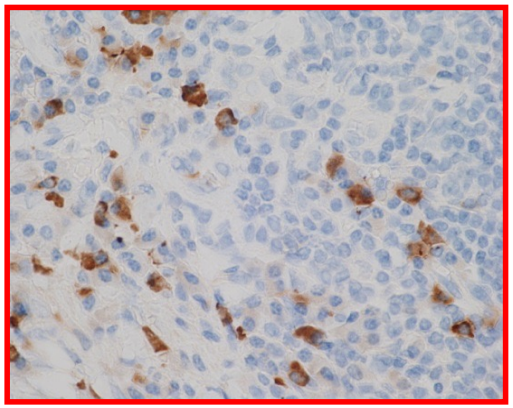
Immunohistochemical staining with IgG and IgG4 antibodies



IgG



IgG4



>10 cells/HPF