

Utility of FDG PET/CT in IgG4-related systemic disease

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1 **ABSTRACT**

2 IgG4-related systemic disease (IgG4-RSD) is an emerging clinical entity about which much
3 remains to be elucidated, in terms of its aetiology, pathogenesis, diagnosis, treatment and
4 outcome. Autoimmune pancreatitis (AIP) and Mikulicz Disease (MD) are the two major,
5 well-studied constituents of IgG4-RSD. AIP and MD have common characteristics of
6 forming tumour-mimicking lesions that consist of lymphoplasmacytic infiltrates and
7 fibrosclerosis with numerous Immunoglobulin G4 (IgG4)-positive plasma cells, as well as
8 various multi-organ manifestations of IgG4-RSD.

9 Fluorine-18 fluorodeoxyglucose positron emission tomography / computed tomography
10 (FDG PET/CT) enables acquisition of whole-body images and provides functional
11 information about disease activity, as such it has a valuable role in staging extent of disease,
12 guiding biopsy and monitoring response to treatment. However, FDG PET/CT is likely to
13 be only one component of the management strategy, and clinical, laboratory, imaging and
14 histological findings are crucial in the overall diagnosis of the condition. At present FDG
15 PET/CT does not have a well-established role in the assessment of patients with IgG4-RSD
16 and future prospective studies are required to more accurately define the cost-effectiveness
17 and clinical impact in this patient group.

18

19 **Keywords**

20 IgG4, autoimmune pancreatitis, Mikulicz disease, PET/CT, FDG

21

1 ***Introduction***

2 Immunoglobulin G4 (IgG4)-related systemic disease (IgG4-RSD) is a new systemic
3 entity characterized by mass-forming lesions in various organs that consist of
4 lymphoplasmacytic infiltrates and fibrosclerosis with numerous IgG4-positive plasma cells
5 [1-3]. For example, the pancreatic manifestation of IgG4-RSD is known as autoimmune
6 pancreatitis (AIP), and salivary gland manifestations include Mikulicz disease (MD) and
7 Küttner tumour [1, 4, 5]. One of the most important peculiarities of IgG4-RSD is that
8 involved lesions often mimic malignancies but respond well to steroid therapy [6]. The
9 epidemiologic information about IgG4-RSD is currently sparse, because it is still an
10 emerging clinical entity and a large number of patients probably remain under-diagnosed
11 [3]. As for AIP, a national-wide survey in Japan in 2002 reported that the prevalence was
12 estimated to be 0.82 per 100,000, predominantly seen in men over the age of 45 years
13 (male : female ratio was 2.85 : 1 in their study population) [7].

14 Fluorine-18 fluorodeoxyglucose positron emission tomography / computed tomography
15 (FDG PET/CT) is one of the imaging techniques commonly used in the field of clinical
16 oncology [8, 9]. Patients with IgG4-RSD have usually undergone FDG PET/CT imaging to
17 differentiate benign from malignant findings [10-12]. However, this technique is
18 increasingly recognized as useful for diagnosis, characterization, and monitoring of

1 response to therapy in patients with inflammatory disorders [13]. This article will provide
2 an overview of IgG4-RSD and the potential role of FDG PET/CT will be illustrated.

3

4 *An overview of IgG4-RSD*

5 *Autoimmune pancreatitis and IgG4*

6 AIP is a unique form of pancreatitis predominantly incident in elderly males in which
7 autoimmune mechanisms are thought to be involved in the pathogenesis [14-16]. AIP is
8 one of the major, well-studied constituents of IgG4-RSD. There exist well developed
9 consensus criteria for the diagnosis of AIP: Asian diagnostic criteria from the Japan-Korea
10 Symposium on AIP and HISTOR criteria from Mayo Clinic [16, 17]. The symptoms in
11 patients with AIP are generally nonspecific. Abdominal pain is usually mild or almost none,
12 though patients occasionally experience acute pancreatitis. The symptoms are rather
13 mimicking those in patients with pancreatic cancer; patients often experience obstructive
14 jaundice and sometimes with back pain and weight loss. Patients with AIP often have
15 diabetes mellitus. They sometimes experience symptoms from accompanying extra-
16 pancreatic lesions [17, 18].

17 AIP is morphologically characterized by irregular narrowing of the main pancreatic duct
18 and diffuse or segmental enlargement of the pancreas [19, 20]. One of the most

1 characteristic imaging features of AIP is a “sausage-like” enlargement of pancreas with
2 “capsule-like” rim, which reflects intense fibrosis around peripancreatic tissue (**Fig. 1**).

3 Dynamic contrast enhanced CT and magnetic resonance imaging (MRI) are outstanding
4 imaging techniques for representing these specific features. Ultrasound sonography (US) is
5 also effective and convenient technique for revealing “sausage-like” pancreas [18]. Main
6 pancreatic duct in the mass is usually narrow. If the duct is found as penetrating through the
7 mass, which is known as “duct-penetrating sign”, it is considered to be helpful finding for
8 differentiating AIP from pancreatic cancer. Although pancreatography is a gold standard
9 for the accurate evaluation of pancreatic ducts, magnetic resonance
10 cholangiopancreatography (MRCP) and US may also support identifying this sign [18].

11 However, AIP sometimes exhibits rather atypical imaging features which make the imaging
12 diagnosis difficult; some patients have only focal pancreatic mass, some patients have
13 irregular and slightly dilated pancreatic duct, and some patients have calcification in the
14 pancreas [18].

15 Patients with AIP often have elevation of serum gamma-globulin, IgG, and IgG4 levels,
16 along with the presence of some autoantibodies. Among these, IgG4 is the best marker for
17 differentiating between AIP and pancreatic cancer [21].

18 The current concept of AIP, including associated extrapancreatic lesions, suggests that it
19 may be a systemic disease, related to IgG4 [1]. However, IgG4 is not entirely specific;

1 some patients with pancreatic cancer have elevated serum IgG4 [22]. Histopathological
2 findings of AIP are characterized by dense lymphoplasmacytic infiltration with fibrosis and
3 obliterative phlebitis, or lymphoplasmacytic sclerosing pancreatitis (LPSP) [23, 24].
4 Immunostaining of LPSP lesions show a number of IgG4-positive plasma cells. On the
5 other hand, idiopathic duct-centric chronic pancreatitis (IDCP), showing infiltration of
6 neutrophils into the epithelium of the main pancreatic duct, has been proposed as another
7 type of AIP [23, 25]. However, as it does not usually show marked IgG4-positive plasma
8 cells infiltration, IDCP cannot be included in AIP as an IgG4-related disease [26, 27].

9

10 *Mikulicz disease and Küttner tumour as IgG4-related diseases*

11 MD is a persistent symmetrical swelling of the lacrimal and salivary glands with non-
12 neoplastic and non-infectious origins (**Fig. 2**). It usually manifests as painless glandular
13 swellings. Patients with MD often do not have keratoconjunctivitis sicca and salivary
14 function [28]. Interestingly, unlike AIP, MD is reported to be predominantly seen in
15 middle-aged or elderly women [28]. Imaging techniques such as CT, MRI, gallium-67
16 scintigraphy, and US are often performed for the evaluation of disease distribution. US
17 findings of bilateral nodal change in submandibular glands are considered as one of the
18 characteristic findings in MD [29].

1 Formerly, MD was regarded as one manifestation of Sjögren syndrome (SS) [30]. Recently,
2 several differences were reported: while patients with MD have enlarged lacrimal and
3 salivary glands, they show rather mild xerostomia and xerophthalmia; raised serum IgG4
4 levels and dense IgG4-positive plasma cell infiltration are common in MD, while not in SS;
5 lymphocytic follicle formation is often observed but lymphocytic infiltration in the ducts
6 (lymphoepithelial lesion) is rarely seen; coexisting disorders such as AIP are often seen;
7 and much better response to steroid therapy is achieved. Therefore, MD, as an IgG4-related
8 disease, would be distinct from SS [4, 31-33].

9 Chronic sclerosing sialadenitis (Küttner tumour) is a fibroinflammatory disease of the
10 salivary glands affecting unilateral or bilateral submandibular glands. It also shows
11 abundant IgG4-positive plasmacytes [5]. Although there remains some discussion about the
12 similarity of the disease with MD, both seem to belong to IgG4-related disease [34, 35].

13

14 *Various multi-organ manifestations with plasmacytic infiltration: IgG4-RSD as an*
15 *integrated entity*

16 In various extra-pancreatic organs of AIP patients, dense infiltration of IgG4-positive
17 plasma cells is often observed as well as CD4- or CD-8 positive T lymphocytes and fibrosis,
18 representative of which is obliterative phlebitis, e.g. sclerosing cholangitis (most often seen
19 in lower bile duct), sclerosing cholecystitis, sclerosing sialadenitis, renal involvement and

1 retroperitoneal fibrosis [1, 2, 36-39]. Moreover, in AIP patients, IgG4-positive plasma cell
2 infiltration can be seen in almost all organs including stomach, duodenum, colon, liver, and
3 bone marrow [40]. Also, identified in patients with MD are a variety of extra-gland lesions
4 such as AIP, tubulointerstitial nephritis, and retroperitoneal fibrosis [33]. These lesions
5 have similar histological and immunohistochemical structures, though there remains some
6 discussion about their differences, such as the extent of fibrosis, the frequency of
7 obliterative phlebitis, and the frequency of lymphoid follicle formation [1, 33, 41, 42].
8 Concomitant lymphadenopathy is also common, which occasionally manifests as systemic
9 lymphadenopathy with polyclonal hyperimmunoglobulinemia, and especially the elevation
10 of IgG and IgE, and positivity of various autoantibodies. Currently, there are five
11 histological subtypes to be considered in IgG4-related lymphadenopathy: Castleman's
12 disease-like morphology, reactive follicular hyperplasia, interfollicular plasmacytosis and
13 immunoblastosis, progressive transformation of germinal centre-like, and inflammatory
14 pseudotumour-like morphology [43]. In addition, a variety of other systemic manifestations
15 have been reported as IgG4-related disease (**Table 1**): e.g. pachymeningitis, hypophysitis,
16 pulmonary inflammatory pseudotumour and interstitial pneumonia, hepatic lesion, breast
17 lesion, prostatitis, inflammatory aortic aneurysm and cutaneous lesions (although it should
18 be noted that no more than a part of each disorder has been reported to have a relationship
19 with IgG4) [44-52]. Therefore, an integrated clinicopathological entity, IgG4-RSD,
20 characterized by extensive IgG4-positive plasma cell and T-lymphocyte infiltration in

1 systemic organs, has been advocated [1, 2, 53]. The importance of the recognition of this
2 entity lies in its remarkable response to steroid therapy. However, it should be stressed that
3 the occurrence of numerous IgG4-positive plasma cells is not specific to this disease [43].

4

5 *The role of FDG PET/CT*

6 *Evaluation of disease distribution to support the diagnosis of IgG4-RSD*

7 As previously mentioned, various manifestations of IgG4-RSD have been reported. Among
8 these, several lesions have characteristic patterns: AIP as diffuse or multi-focal pancreatic
9 swelling (**Fig. 3**); MD as symmetric swelling of lacrimal and submandibular glands; and
10 retroperitoneal fibrosis as periaortic or periureteral / peripelvic renal mass lesions [1, 11, 33,
11 39]. The individual lesions are not pathognomonic for IgG4-RSD, but combinations of
12 these suggest the possibility of the disease.

13 Whole-body FDG PET/CT provides excellent information about the distribution of disease.

14 It would be a useful tool for detecting systemic involvement in patients with IgG4-RSD.

15 Nakajo et al. reported that PET scans revealed intense FDG uptake by AIP in all six
16 patients and that abnormal FDG uptake by extrapancreatic lesions were observed in five of
17 the six patients [12]. Although it is hard to differentiate malignancy from inflammatory
18 lesions even if using dual-time-point imaging, the understanding of disease distribution

1 obtained by using PET/CT may provide important information for distinguishing AIP from
2 pancreatic cancer. Ozaki et al. studied 15 patients with AIP and 26 patients with pancreatic
3 cancer and stated that the maximum standardized uptake value (SUV) did not differ
4 significantly in either the early or delayed phase between AIP (the median max SUV was
5 4.6 in the early phase and 5.4 in the delayed phase) and pancreatic cancer (the median max
6 SUV was 5.3 in the early phase and 6.5 in the delayed phase) [11]. However, they stated
7 that multiple foci in the pancreas were significantly more often observed in AIP (8 of 15
8 cases) than in pancreatic cancer (1 of 19 cases). Also, hilar lymphadenopathy was
9 significantly more frequent in patients with AIP (9 of 15 cases) than in patients with
10 pancreatic cancer (3 of 26 cases). Concomitant FDG uptake in the lacrimal gland, salivary
11 gland, biliary duct, retroperitoneal space, and prostate were seen only in patients with AIP
12 in their study [11]. Therefore, it seems that concomitant FDG uptake in these organs may
13 support the diagnosis of AIP (**Fig. 4**). The predominance of FDG PET/CT about the
14 diagnostic accuracy compared with CT or MRI has yet to be investigated. Gallium-67
15 scintigraphy and single-photon emission tomography (SPECT) / CT are also feasible
16 imaging techniques for the evaluation of disease distribution in patients with IgG4-RSD [54,
17 55], though PET/CT has an advantage in spatial resolution and signal-to-noise ratio.

18

19 *Guiding minimally invasive tissue diagnosis to support the diagnosis of IgG4-RSD*

1 Intensity of FDG uptake cannot always distinguish between malignant and benign
2 disorders; however, it generally reflects glucose metabolism and thereby disease activity.
3 Therefore, FDG PET/CT can be a helpful adjunct for detecting an adequate biopsy site.
4 Moreover, minimally invasive biopsy can be accomplished. For instance, the identification
5 of an evident submandibular lesion can avoid the need for the biopsy of periaortic fibrosis
6 (**Fig. 5**).

7

8 *Pointing out specific condition for which steroid therapy is indicated*

9 Steroid therapy is indicated for symptomatic IgG4-RSD, that is, AIP with obstructive
10 jaundice or abdominal pain, MD with xerophthalmia and xerostomia, and other associated
11 symptomatic lesions such as retroperitoneal fibrosis, interstitial pneumonia and
12 tubulointerstitial nephritis [56, 57]. Various organ manifestations can result in critical
13 conditions. In such cases, providing an adequate diagnosis of IgG4-RSD is made, the
14 immediate introduction of steroids leads to better convalescence and outcome. For example,
15 IgG4-related tubulointerstitial nephritis causes acute renal failure that prohibits the use of
16 IV contrast agents. If FDG PET/CT is used to make the diagnosis, steroid therapy can bring
17 about a quick recovery of renal function (**Fig. 6**) [58]. Actually, IgG4-RSD is often
18 concurrent with asthma, which causes difficulty in the use IV contrast media [33]. FDG
19 PET/CT can be safely employed for the imaging of such patients. However, IgG4-RSD,

1 and especially AIP, is also frequently concurrent with diabetes mellitus [1], which should
2 be taken into account when using FDG PET/CT. For patients with diabetes, specific
3 preparations before examinations are required for controlling plasma glucose and serum
4 insulin levels that considerably affect biological distribution of FDG [59], such as extensive
5 skeletal muscle accumulation.

6

7 *Monitoring response to therapy*

8 After 2–4 weeks at the initial steroid dose (0.6mg/kg/day oral prednisolone as
9 recommended by Japanese AIP guidelines), the dose should be reduced (by 5mg) every
10 week based on changes in the clinical manifestations, biochemical blood tests (such as liver
11 enzymes and serum IgG or IgG4 levels), and repeated imaging findings. After dose is
12 reduced over a period of 2–3 months, a maintenance dose (2.5-5mg/day) is recommended
13 to prevent relapse [56]. After stopping medication, patients should undergo follow up for
14 occurrence of relapse. Maintenance steroid therapy should be planned within at least 3
15 years, in cases with radiological and serological improvement [56]. Patients should not
16 interrupt their medication immediately even though they have become asymptomatic. Long
17 term outcome of patients with IgG4-RSD has yet to be well-analyzed. Relapse of IgG4-
18 RSD, exocrine or endocrine dysfunction, steroid induced glucose intolerance, and possible
19 associated malignancy are supposed to have an influence upon the patients' outcome [56].

1 Imaging procedures for the use of monitoring therapy response are still challenging. FDG
2 PET/CT may have a potential for an effective imaging technique for monitoring steroid
3 response in IgG4-RSD patients (**Fig. 7**). The advantage of PET is that SUV is available as a
4 semi-quantitative score to evaluate the activity of inflammatory disease. Matsubayashi et al.
5 reported that in 11 patients with AIP who underwent FDG PET before and after steroid
6 therapy FDG accumulation was diminished in almost all systemic lesions, with the mean of
7 maximum SUV in the pancreatic lesion from 5.12 to 2.69, accompanied by the decrease of
8 serum IgG and IgG4 levels [60]. However, it should be kept in mind that hyperglycemia
9 due to diabetes mellitus, which is often accompanied with AIP patients, can influence SUV,
10 usually with underestimation [61]. Performing PET/CT whilst on steroids could over-
11 estimate the response. There have been no prospective studies that compare the
12 predominance of FDG PET/CT to other imaging techniques or assessing symptomatic
13 response. It should also be noted that currently there is no consensus about the duration of
14 steroid therapy [56]. Therefore, currently there is still no consensus for the use of FDG
15 PET/CT for steroid therapeutic strategy, though several reports have mentioned its potential
16 value. The optimal timing of PET/CT after steroid therapy remains unclear. As a matter of
17 course, there is currently no consensus that maintenance therapy is stopped by the
18 disappearance of FDG uptake.

1 Another advantage of FDG PET/CT is that it may have the ability of identifying disease
2 relapse earlier than other imaging techniques. The relapse rate of AIP is reported to be 10%
3 to 53% [56]. In patients with a relapse of IgG4-RSD, elevated serum IgG4 or IgG, elevated
4 soluble IL-2 receptor or immune complex, complement consumption are often observed.
5 Impaired exocrine function or other organ dysfunction is also a sign of disease relapse.
6 Currently, CT, MRI, and US are often examined in patients with the signs of relapse, where
7 the evidence of relapse is shown as morphological enlargement. However, one of the
8 important characteristic of IgG4-RSD is that relapse can occur in different organs from the
9 primary lesion site [56], some of which these conventional imaging techniques may be
10 difficult to identify. FDG PET/CT, as a whole body imaging technique, may be the optimal
11 technique for detecting such an unexpected activated disease relapse at a glance. On the
12 other hand, it should be noted that there exists no consensus about the optimal timing or
13 frequency of PET/CT examinations for surveillance for relapse of IgG4-RSD.

14

15 *Outstanding issues related to differential diagnosis*

16 The differential diagnosis of IgG4-RSD from other autoimmune diseases or
17 lymphoproliferative disorders (e.g. multicentric Castleman's disease or idiopathic
18 plasmacytic lymphadenopathy) is important [33, 43]. The most important problem is the
19 differential diagnosis from malignant lymphoma, both radiologically and histologically.

1 IgG4-related lymphadenopathy with atypical lymphoplasmacytic and immunoblastic
2 proliferation type shows histological characters often confused with malignant lymphoma,
3 especially angioimmunoblastic T-cell lymphoma, which typically presents with polyclonal
4 hypergammaglobulinemia [62, 63].

5 Moreover, there are reports about “IgG4-related MALT lymphoma” or “IgG4-producing
6 lymphoma” in ocular adnexal regions [43]. MALT lymphoma often arises from the lesion
7 with a background of chronic inflammation, often autoimmune disorders that result in
8 accumulation of extranodal lymphoid tissue. Some authors advocate that patients with
9 ocular adnexal IgG4-related disease might be at an increased risk of developing MALT
10 lymphoma. However, it should be also noted that IgG4-related MALT lymphoma is rarely
11 reported in the other organs [43].

12 The development of lymphoma during the follow-up of IgG4-RSD is occasionally
13 experienced (**Fig. 8**). Takahasahi et al. studied 111 patients with IgG4-RSD and during
14 their 331 patient-years of observation 3 patients developed non-Hodgkin lymphoma 3- 5
15 years after the diagnosis of IgG4-RSD [64]. However, further studies are needed to
16 elucidate the hypothesis that patients with IgG4-RSD are at an increased risk of developing
17 lymphoma.

18

19 *Future prospects*

1 In this article, we have discussed how to make use of FDG PET/CT for the clinical
2 evaluation of IgG4-RSD. However, IgG4-RSD is not a definitively established disease
3 entity. Several synonyms such as “IgG4-related sclerosing disease” or “IgG4-positive
4 multiorgan lymphoproliferative syndrome” are used [1, 33]. It remains controversial
5 whether these are entirely the same concept. It should be emphasized that no specific
6 diagnostic criteria currently exist for IgG4-RSD. Moreover, most studies have
7 retrospectively investigated mainly symptomatic lesions, so these may not have been fully
8 objective. For instance, patients with MD are rarely examined by abdominal scanning and
9 those with AIP often are not examined using head and neck scanning. Pathogenesis and
10 pathophysiology of IgG4-RSD are still unsolved. Several authors suggested that regulatory
11 T cells (Tregs) seem to play an important role in progression as well as in induction of the
12 disease and that IgG4 or IgG4-immune complexes are unlikely to be pathogenetic factors
13 but may be anti-inflammatory factors [65-67]. Therefore, the role of serum IgG4 in the
14 diagnosis of IgG4-RSD is currently controversial, whereas the sensitivity and specificity of
15 raised serum IgG4 in the diagnosis of AIP were reported to be 80% and 98% respectively,
16 the highest diagnostic value among all serological diagnostic methods [18]. Hence, full
17 details about IgG4-RSD remain unclear.

18 Although FDG PET/CT is only one component in the diagnostic pathway of this
19 challenging condition, the advantage of PET/CT is that it can provide whole-body images

1 and (semi-) quantitative scores that benefit objective information. Though there is to date a
2 paucity of data on the use of FDG PET/CT in this patient group, FDG PET/CT might have
3 a potential to help uncover more detail radiological aspects of IgG4-RSD. Besides, the
4 impact of FDG PET/CT on patient management and its cost-effectiveness are unclear.
5 Patient exposure to radiation must be optimized. The relatively high radiation dose hinders
6 the use of FDG PET/CT from repeated assessments of non-malignant disease [68].
7 Therefore, well designed prospective studies would be required to more accurately define
8 the optimal use of FDG PET/CT.

9 Besides FDG, new PET tracer for more specific mechanism of uptake in the immune
10 activation is expected in the future. Fluorine-18 fluoroarabinofuranosyl cytosine (FAC), a
11 novel PET probe for the deoxyribonucleotide salvage pathway, is reported to enable
12 visualization of lymphoid organs and to be sensitive to localized immune reaction in a
13 mouse model of antitumour immunity [69]. The use of FAC PET may have a potential to
14 offer new insights in the evaluation of autoimmune disorders [13], though it would be
15 difficult to allow confident distinction between inflammation and malignancy.

16

17 ***Conclusions***

18 In this article, an overview of IgG4-RSD has been presented and the potential roles of FDG
19 PET/CT have been illustrated. It can be useful for diagnosis, recognition of activated

1 lesions, monitoring of therapy response and detecting relapse. There remain several
2 unresolved problems, among which the most serious is the differential diagnosis from
3 malignant lymphoma. Since it is not yet a definitively established disease entity, we
4 propose using FDG PET/CT for promoting more detailed prospective clinical studies about
5 IgG4-RSD.

6

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- 18

1 **Fig. 1** A case of autoimmune pancreatitis (AIP). An axial image from a contrast-enhanced
2 CT scan is shown. Diffuse pancreatic swelling with a capsule-like rim is seen (arrows).

3

4 **Fig. 2** A case of Mikulicz disease (MD). Axial images from an unenhanced CT scan show
5 (a) diffuse bilateral swelling of lacrimal glands and (b) diffuse bilateral swelling of
6 submandibular glands (arrows).

7

8 **Fig. 3** A case of AIP. (a) A Maximum intensity projection (MIP) image from FDG PET
9 and (b) oblique coronal reconstruction from fused PET/CT images are shown. Multifocal
10 lesions with intense uptake are seen in the pancreatic head and the pancreatic tail (arrows),
11 and are helpful features for distinguishing AIP from pancreatic cancer. Maximum SUVs
12 were 6.5 at the pancreatic head lesion and 5.5 at the pancreatic tail lesion.

13

14 **Fig. 4** A case of AIP. A MIP image from FDG PET shows diffuse uptake in the pancreas
15 and focal uptake in the hilar nodes and the gallbladder (arrows), representing a typical
16 distribution in AIP. Maximum SUV at the pancreatic lesion was 4.6.

17

1 **Fig. 5** A MIP image of FDG PET in a case of IgG4-RSD. IgG4-RSD was suspected
2 because of periaortic fibrosis and hilar lymphadenopathy. In addition, PET showed a
3 submandibular lesion (thick arrow), where IgG4-related sialadenitis was proved by biopsy.
4 (Parotid tumour (thin arrow) had been proven to be benign beforehand, using fine-needle
5 aspiration cytology, though its detailed histology remained unclear.)

6

7 **Fig. 6** A MIP image of FDG PET in a case of IgG4-related sclerosing sialadenitis (proved
8 by submandibular biopsy beforehand). The image shows diffuse intense uptake in bilateral
9 kidneys that suggests IgG4-associated nephropathy, the probable cause of acute renal
10 dysfunction. Activated lesions with intense FDG uptake are also seen in bilateral
11 submandibular glands, left supraclavicular lymph nodes, bilateral hilar and mediastinal
12 lymph nodes, periaortic soft tissue, and prostate.

13

14 **Fig. 7** MIP images of FDG PET in a case of IgG4-RSD (a) at the initial scan and (b) at
15 week 4 after steroid induction. Intermediate FDG uptake by the retroperitoneal lesion
16 (arrow) has vanished after steroid therapy. Maximum SUV in the retroperitoneal lesion was
17 3.7 at the initial scan and 2.2 after steroid therapy.

18

1 **Fig. 8** A MIP image of FDG PET in a case of B-cell non-Hodgkin lymphoma developed
2 during follow-up of IgG4-RSD. Although no active lesion was seen in the follow-up scan
3 after steroid therapy for IgG4-RSD (not shown), bulky lymphoma abruptly appeared,
4 together with extranodal lesions such as multi-focal osseous involvement, during following
5 8 months.

6

7

Fig. 1



Fig. 2(a)

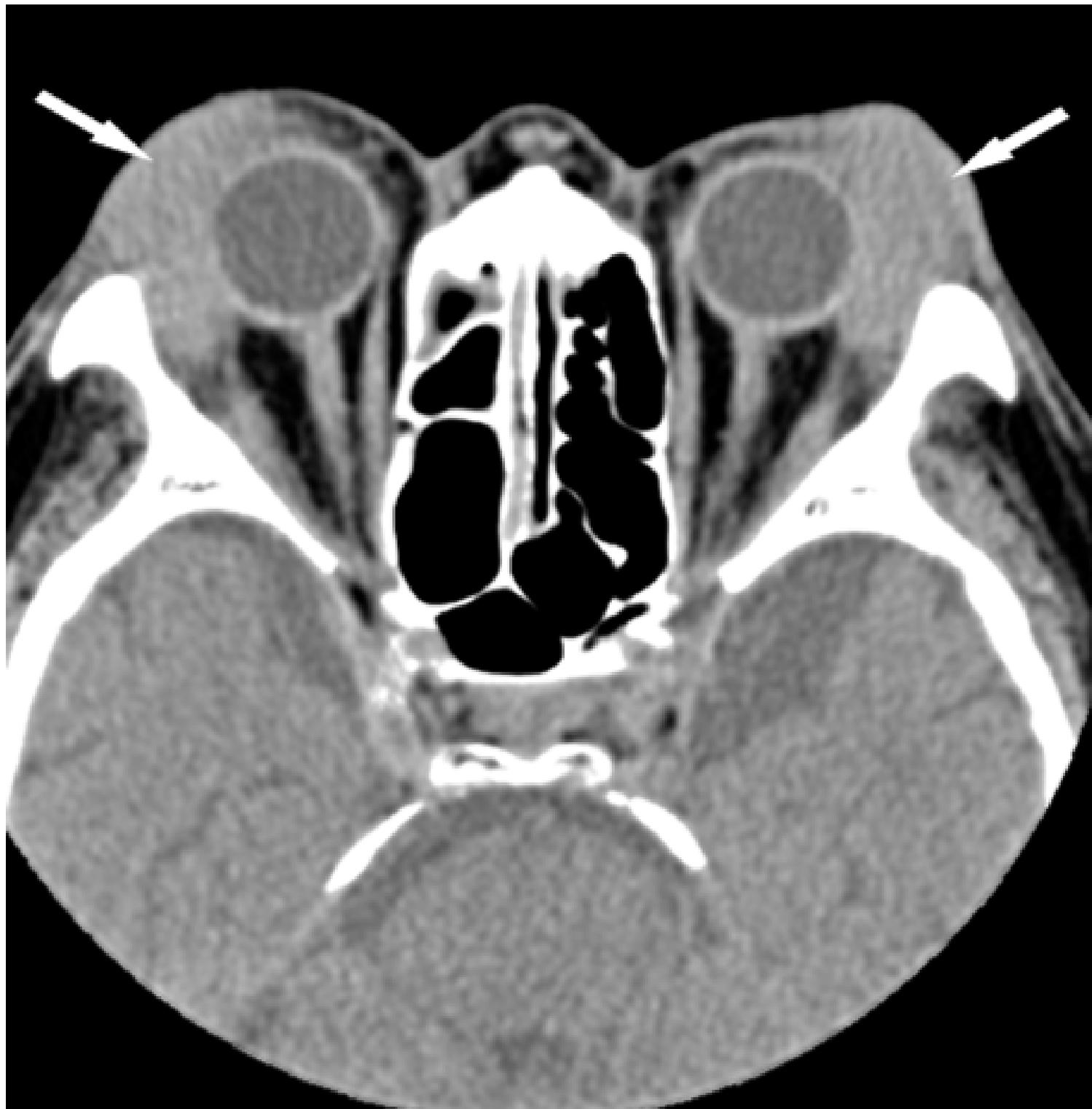


Fig. 2(b)

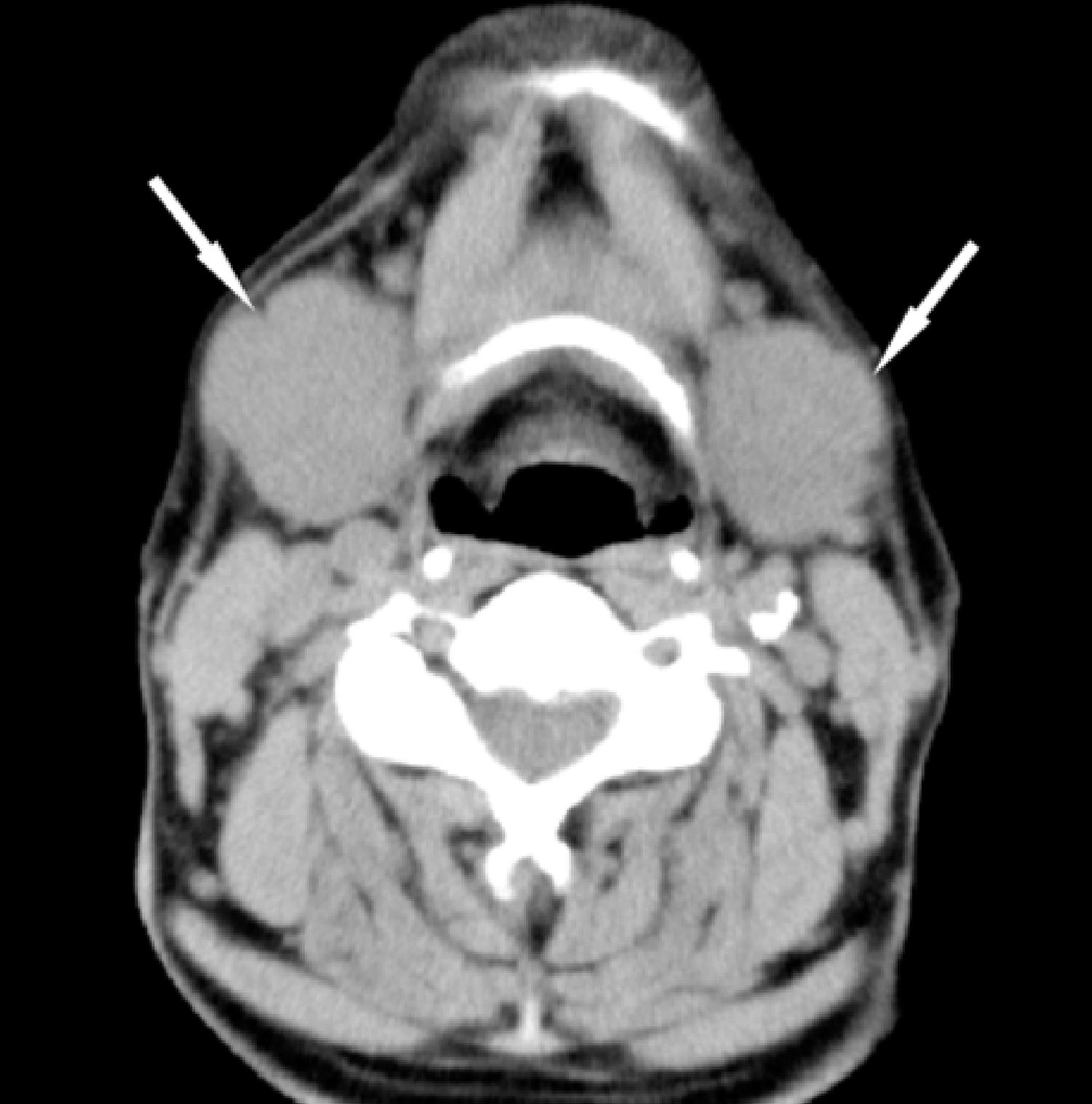


Fig. 3(a)



Fig. 3(b)

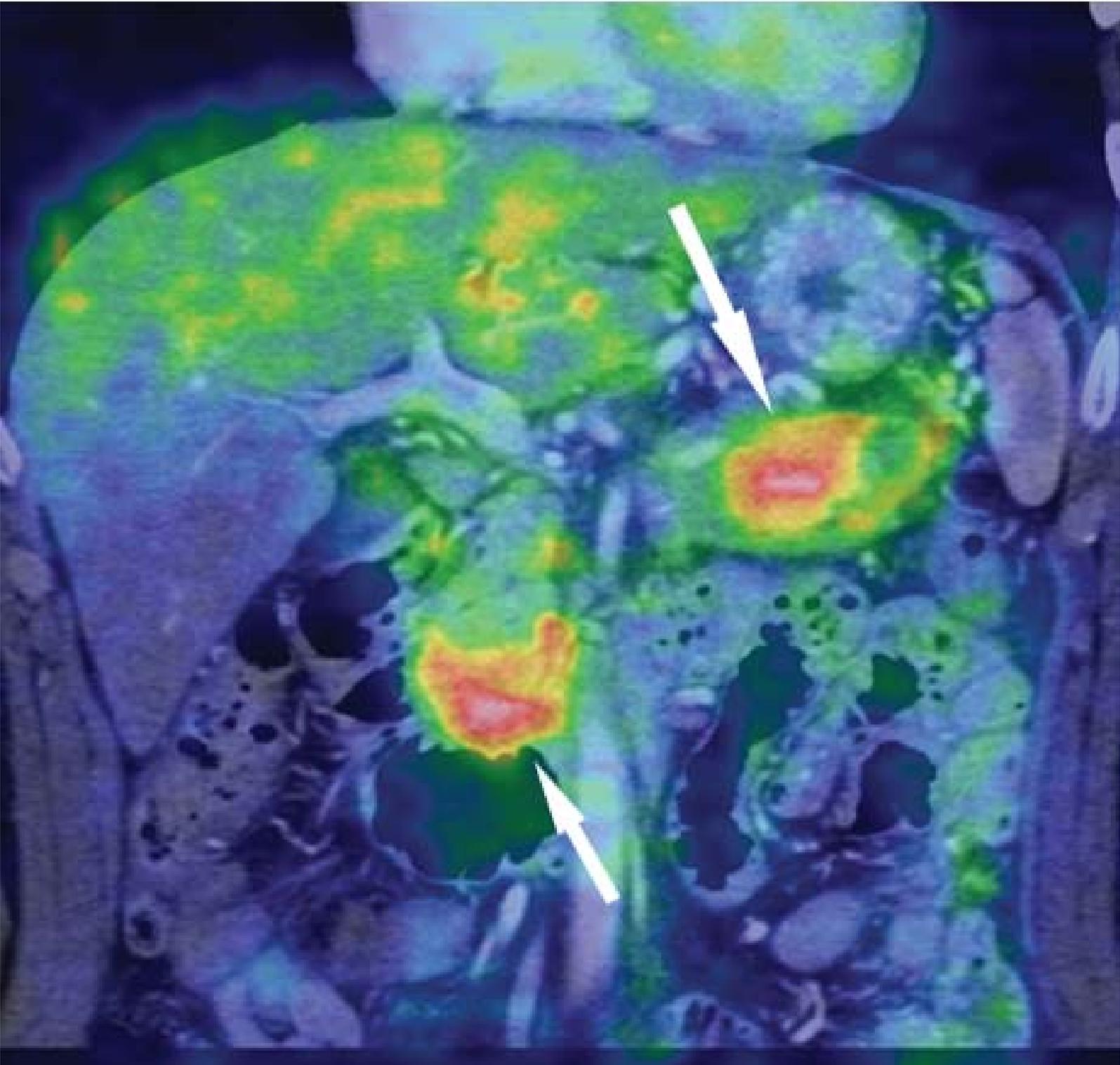


Fig. 4

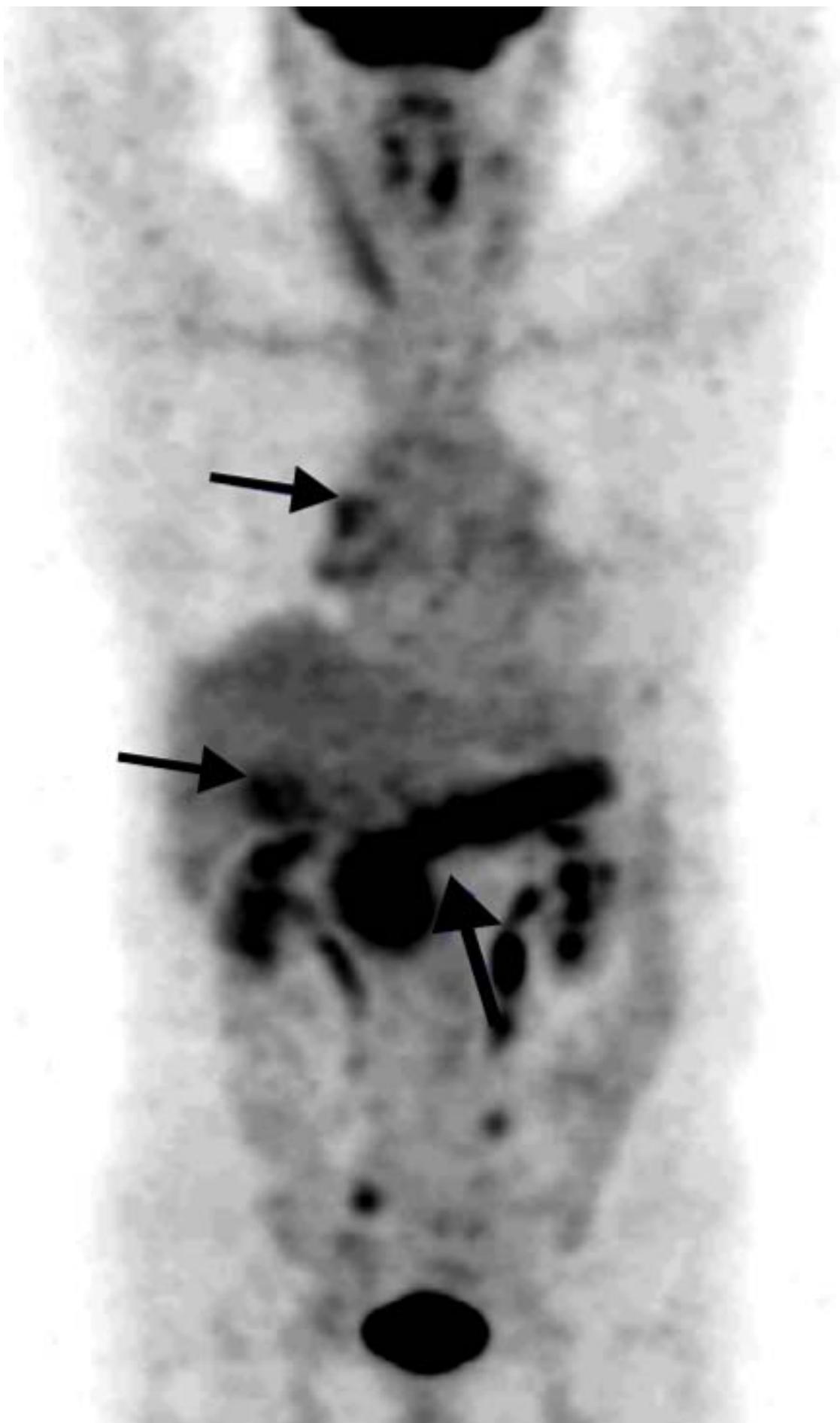


Fig. 5



Fig. 6



Fig. 7(a)



Fig. 7(b)

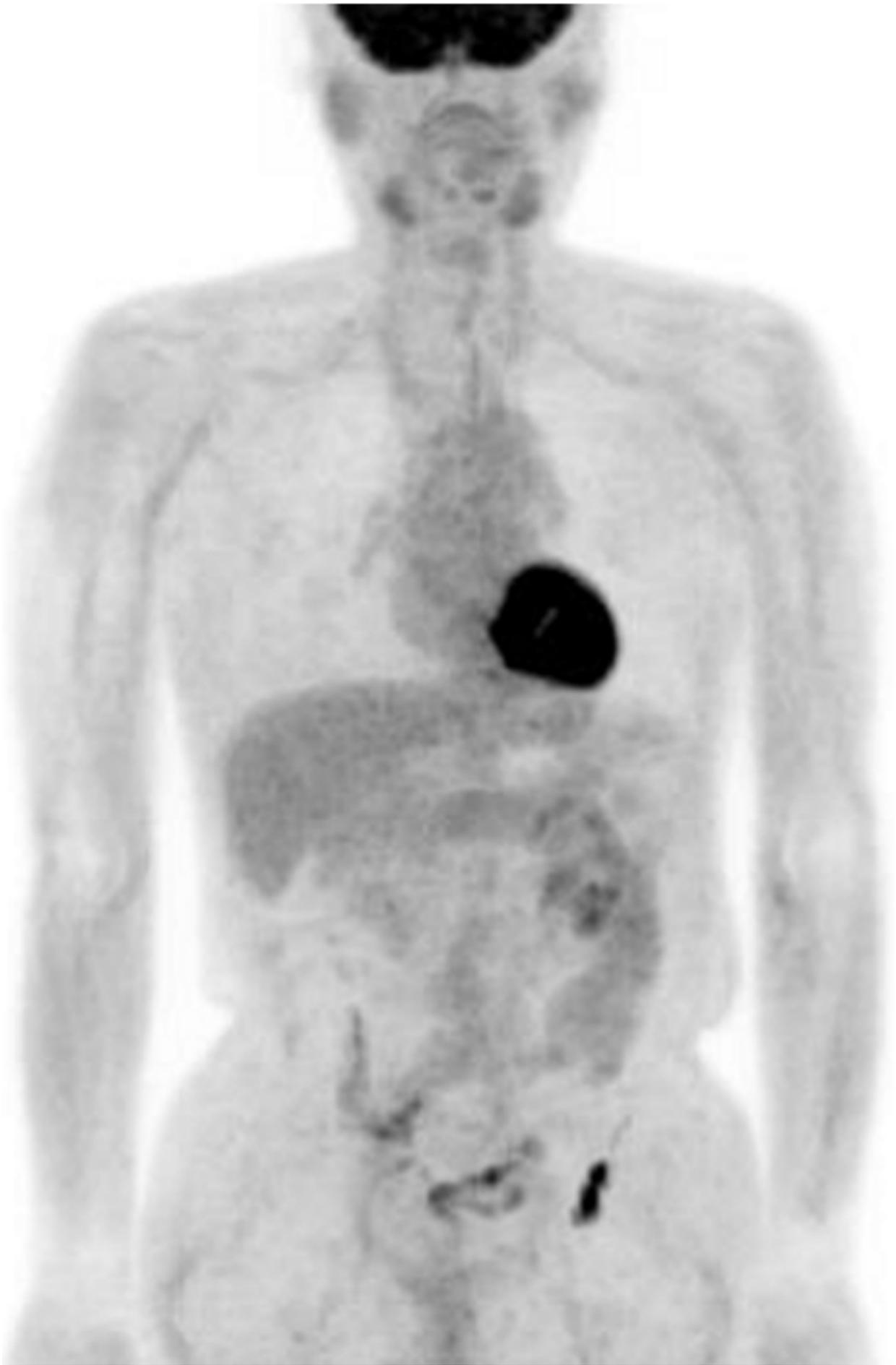
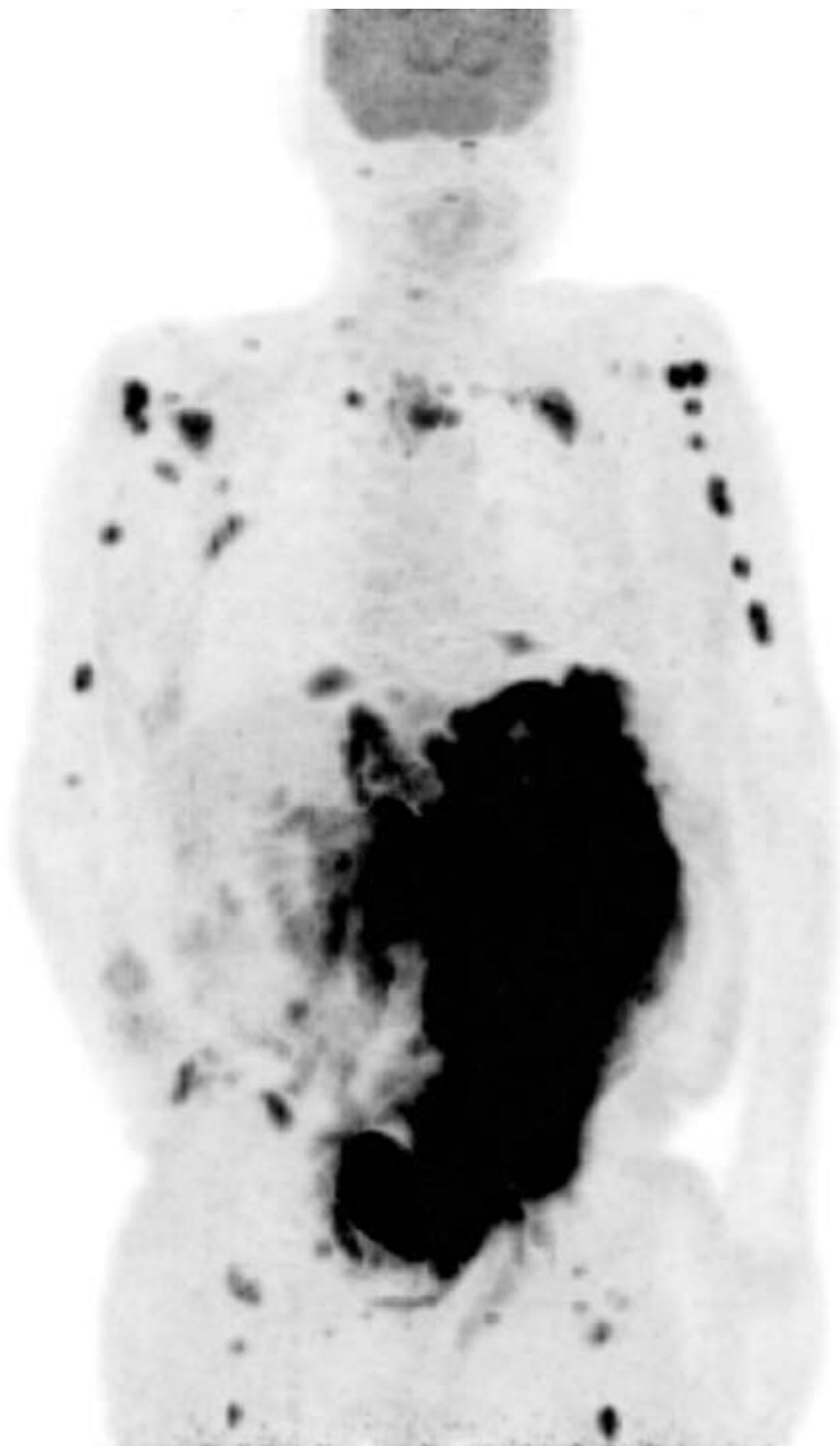


Fig. 8



- 1 **Table 1** Various multi-organ manifestations in IgG4-RSD. Note —the diseases listed are
 2 not always the constituents of IgG4-RSD.

Organs	Previously reported IgG4-related lesions
Meninges	Pachymeningitis
Hypophysis	Hypophysitis
Ocular adnexa / Lacrimal gland	Orbital inflammatory pseudotumour Mikulicz disease
Salivary gland	Mikulicz disease Sclerosing sialadenitis (Küttner tumour)
Thyroid gland	Riedel thyroiditis
Lung	Plasma cell granuloma (Inflammatory pseudotumour) Interstitial pneumonia
Breast	Inflammatory pseudotumour
Pancreas	Autoimmune pancreatitis
Liver	Inflammatory pseudotumour Hepatopathy

Biliary duct / Gallbladder	Sclerosing cholangitis / Sclerosing cholecystitis
Retroperitoneum	Retroperitoneal fibrosis
Aorta	Inflammatory aortic aneurysm (Periaortic fibrosis)
Kidney	Tubulointerstitial nephritis
Prostate	Prostatitis
Lymph node	Lymphadenopathy
Skin	Cutaneous pseudolymphoma
