

RHEUMATOLOGICAL ASPECTS OF IgG4-RELATED DISEASE

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Abstract. *Immunoglobulin G4-related disease (IgG4-RD) is an immune-mediated fibro-inflammatory disorder characterized by a tissue IgG4(+) plasma cells infiltration leading to fibrosis and destruction of the involved organs. The IgG4-RD scope includes all organs and systems but within the review only the actual diagnostic and therapeutic data concerning disease localisations in the lacrimal and salivary glands, kidneys, retroperitoneum, lungs and aorta and arteries are included because they are also a terrain of a rheumatological pathology – vasculitides, Sjogren's syndrome, SLE, systemic sclerosis and so on.*

Key words: *IgG4-related disease, diagnosis, treatment*

Immunoglobulin G4-related disease (IgG4-RD) is a systemic immune-mediated condition presenting itself with tumefactive lesions of one or more organs, caused by a tissue infiltration with IgG4(+) plasma cells with a following fibrosis, which often but not always is accompanied with an elevated serum level of IgG4.

IgG4-RD is accepted as a new disease entity in view that its clinical characteristics is ascertained in the beginning of the present century [16, 22]; in 2011 it is already authorized with consensually approved term and diagnostic criteria [55], pathology [15] and nomenclature [52] and subsequently – guidance statement on the management and treatment [27] and classification criteria [61].

IgG4-RD could be considered as an old disease, too, because at present it includes also 13 diseases familiar from the 20th c., but some of them even from the 19th c., which have been regarded earlier as particular illnesses (Table 1).

Table 1. Conditions once regarded as individual disorders now recognized to be part of IgG4-related disease

- Autoimmune pancreatitis
- Eosinophilic angiocentric fibrosis
- Hypertrophic pachymeningitis
- Idiopathic hypocomplementemic tubulointerstitial nephritis
- Inflammatory pseudotumour
- Küttner's tumour
- Mikulicz's disease
- Multifocal fibrosclerosis
- Periaortitis and periarteritis
- Inflammatory aortic aneurysm
- Retroperitoneal fibrosis (Ormond's disease)
- Riedel's thyroiditis
- Sclerosing mesenteritis

The unifying of the “old” and “new” forms of the disease is based on the sharing analogous pathology, clinical assessment, serology and therapy.

Pathology: 1. Dense infiltrate of lymphocytes (T-cells > B-cells) and plasma cells with sometimes generation of germinative follicles; eosinophils and basophils can also present. 2. Storiform fibrosis – collagen fibres radiating from a centre woven into the infiltrated tissue. 3. Obliterative phlebitis – partial or complete obliteration from lymphocytes and plasma cells within the wall and lumen of medium-sized veins. The abundance of IgG4(+) plasma cells is a key sign, whereas fibrosis or phlebitis could be missing in the early stage or in some organ localizations. The presence of a neutrophil infiltration, necrosis or granuloma is inconsistent with IgG4-RD [15, 22, 70].

Clinical picture: every organ can be affected (exception – brain parenchyma) alone or in combination. The evolution (simultaneously or consecutively) is slow, sometimes haltingly. The affected organ is enlarged and congested, which is determinable visibly, by palpation or imaginably (CT, MRI, PET/CT). The symptoms – general (fatigue, weight-loss) and specific for each organ – are conditioned by the developing dysfunction and insufficiency [3, 23, 60].

Serology. The increased serum level of IgG4 > 135 mg/dl or the ratio IgG4(+) plasma cells to IgG [1, 2, 3, 4] (+) plasma cells > 40% have sensitivity 85% and specificity 93% towards IgG4-RD [65]. These cut-offs are not reached in 20-45% in a definite IgG4-RD but are fulfilled in 15-20% in another disorders. Given that IgG4 is not accepted as an independent diagnostic marker, however, it is useful for assessment of the disease activity and of a treatment effect [5, 10, 12, 60].

Therapy. All organ forms of IgG4-RD respond well to a treatment with glucocorticoids (GCs) under condition that the fibrosis is not quite advanced.

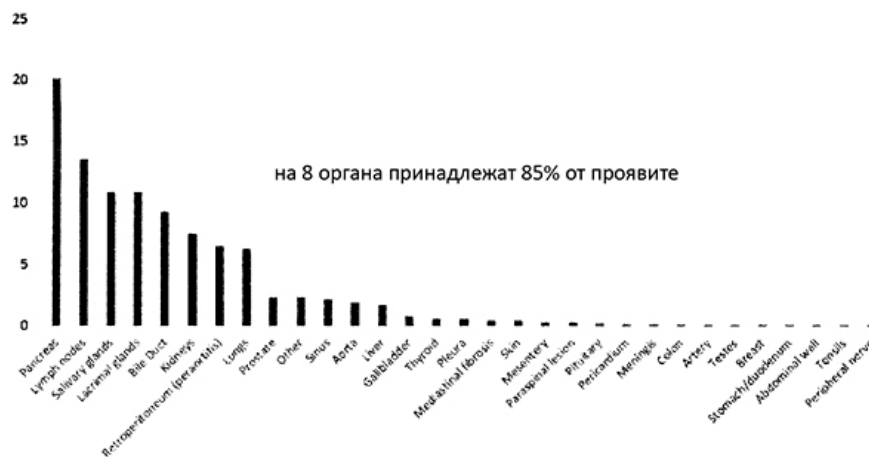


Fig. 1. Proportion of organ manifestations in IgG4 SB (Miyabe et al.) (1717 organs manifestations in 758 patients)

- The IgG4-RD-involvement of all organs, systems and tissues makes this disease an object of all clinical specialities [8, 15, 23, 52]. As it is illustrated at Fig. 1, the particular organs are damaged differently often, and from that it follows a different engagement of the particular specialities with IgG4-RD. Amidst the most often IgG4-RD-lesions are these of the salivary and lacrimal glands, kidneys, retroperitoneum, lungs and aorta, which are of the terrain of rheumatological pathology. The inevitable differential-diagnostic considerations and eventual therapeutic differences necessitate the rheumatologist's knowledge on the aforementioned organ forms of IgG4-RD.

IGG4-RELATED DACRYOADENITIS AND SIALADENITIS

The lacrimal and salivary glands are a basal substratum of the described in 1888 Mikulicz's disease (MD) as well as of the formulated in 1933 Sjogren's syndrome (SS), both united by Morgan and Castleman in the middle of the past century, whereupon MD is accepted as a variant of SS. In the last decades, however, a sufficiency of data are piled up [1, 3, 14, 22, 33, 41, 55, 60, 67] showing that MD and SS in reality are two different disease entities are piled up. In the next statement the name "MD" will be replaced by "IgG4-related dacryoadenitis and sialadenitis" (IgG4-DA/SA), unifying two nomenclature forms of IgG4-RD, where the second one includes

the submandibular, sublingual and parotid salivary glands. Further, the characteristic features of IgG4-DA/SA and SS are juxtaposed.

- IgG4-DA/SA affects almost equally men and women, whereas SS is 15-20 times more frequent in women.

- In SS xerophthalmia and xerostomia are leading symptoms, when in IgG4-DA/SA they occur only in a part of the patients, in later stage and in milder degree. In SS a specific multiple circular caries leading to early adentia develops, whereas in IgG4-DA/SA the caries is rarer, from common type and with considerably longer teeth preservation. The oral mucosa and tongue in IgG4-DA/SA are with almost normal look, while in SS the tongue is dry, with fissures, often with mycotic infection.

- In IgG4-DA/SA a fundamental sign is the symmetric painless enlargement at first of submandibular glands, then of the lacrimal, parotid and sublingual ones, when in SS only a parotid enlargement occurs, albeit rarely (in 10-15%) and in later stage.

- IgG4-DA/SA is often accompanied by allergic rhinitis, bronchial asthma, autoimmune pancreatitis, sclerosing cholangitis, interstitial nephritis, whereas in SS arthralgia occurs more often.

- Both diseases differ from one another in relation to the immunological markers; elevated values of anti-SS-A (Ro) and anti-SS-B (La) antibodies, of RF and ANA are established more frequently in SS, whereas in IgG4-DA/SA it concerns IgG4 and IgE.

- Histologically in a biopsy of labial minor salivary or of submandibular gland in both diseases a diffuse lymphoid infiltration is found out, but in IgG4-DA/SA it is denser and in SS – looser. Moreover, in IgG4-DA/SA mostly the interstitium is infiltrated, the acini stay intact and secreting, the ducts, only partially infiltrated, are harmed by proliferation of their epithelium with a result – difficulty of the salivary flow. In SS the infiltration affects the acini with a following atrophy and sclerosis, the ducts are aggressively infiltrated, have a proliferating epithelium and destructed basal membrane [2, 3, 33, 41, 60, 67, 70].

- Immunohistologically IgG4(+) plasma cells in the infiltrates are established in both diseases, however, in SS they are scarce, in IgG4-DA/SA – abundant and exceeding the diagnostic cut off for

Table 2. Clinical and laboratory comparison between IgG4-DA/SA (n = 64) and SS (n = 31) (Masaki et al., 2009)

indicator	IgG4-CE n = 64	SS n = 31	P	indicator	IgG4-CE n = 64	SS n = 31	P
xerophthalmia	32.8	< 93.5	< 0.001	RF	26.6	< 87.1	< 0.001
xerostomia	37.5	< 87.1	< 0.001	ANA	23.4	< 90.3	< 0.001
arthralgia	15.6	< 48.4	0.001	SS-A/Ro	1.6	< 100.0	< 0.001
allergic rhinitis	40.6 >	6.5	0.001	SS-B/La	0	< 100.0	< 0.001
autoimmune pancreatitis	17.2 >	0	0.014	IgG-mg%	2960.1 >	2473.4	0.042
interstitial nephritis	17.2 >	6.5	0.210	IgG4-mg%	1155.3 >	23.5	< 0.001
interstitial pneumonitis	9.4	< 32.3	0.008	IgE-IU/L	307.4 >	15.3	< 0.005

lacrimal and salivary glands > 100 IgG4(+) plasma cells per high power field (HPF) and simultaneously the ratio IgG4(+) plasma cells/IgG1,2,3,4(+) plasma cells > 40% [2, 15, 33, 41, 67, 70].

– At last, a contribution to differential diagnostics can give the therapeutic course with GC – complete or partial restoration of the gland secretion in IgG4-DA/SA, and no effect in SS, respectively.

Except for SS, IgG4-DA/SA has to be differentiated from chronic inflammations of the lacrimal and salivary glands, sialolithiasis, lymphoma, cancer, sarcoidosis, granulomatosis with polyangiitis (GPA) (Wegener), amyloidosis, Castleman's disease, etc. In 2012 Japanese authors recommend diagnostic criteria for MD [55], renamed in 2017 as for IgG4-DA/SA [56], which include clinical, serological and histological markers. For the present, the criteria are not validated.

The treatment of IgG4-DA/SA until now has been an object of only two studies. In the first one [33], including 38 patients, the GC in a dose 10-30 mg/day are used in the majority of the patients and in up to 40-60 mg/day – in the cases with involvement of internal organs. A marked improvement of the clinical signs and symptoms was recorded; however, during tapering GC dose recurrence was seen in 39%. Ultimately, a maintenance dose of 2.5-10.0 mg/day is used in almost all (37/38) patients. In the second study on 7 patients) [67] GC in an initial dose 40 mg/day caused a measured increase of salivary secretion in 80%, a significant ($p < 0,05$) decrease of IgG4 concentration in blood serum, respectively. Follow-up of the effect is not available.

IGG4-RELATED KIDNEY DISEASE

The frequency of IgG4-related kidney disease (IgG4-RKD) amidst all IgG4-RD patients is determined from 7.0 to 24.6% (4,24,46,60) but the data of the large-scale study of Wallace [62] – 15.6% (77 from all 493 patients with IgG4-RD) is considered

most reliable. Rarely (0-17%) IgG4-RKD is an isolated finding; contrariwise – in the prevailing part of the cases (83-100%) it occurs in combination with an involvement of others organs, on average 3,4 (salivary glands > lymph nodes > lung > lacrimal glands > pancreas, etc). The ratio of male to female patients is 3 : 1 [25, 36, 49].

Pathologically the tubulointerstitial nephritis (TIN) is the most common and characteristic – immune complexes in the tubular basement membrane and IgG4(+) plasma cells infiltration and storiform fibrosis in the interstitium. The more rare forms are membranous glomerulonephritis (MGN), renal capsulitis, pyelitis, periureteritis, arteritis and renal pseudotumor, which in most cases are combined with TIN [13, 24, 37, 46, 49, 72].

The clinical course is asymptomatic for a long time but later and rarely – with not typical pains in back or abdomen, oliguria, weight loss, edema. The urinalysis is normal, however, in the presence of MGN it can be pathologic (hematuria > proteinuria). Blood investigations reveal as follows: hypercreatinemia and anemia in the later stages but very early a rich immunological pathology – increase of the total IgG (in 80-90%), especially of IgG4 (in 90-100%), IgE (60-70%), eosinophilia (30-40%), ANA (30%), but a decrease of serum complement (CH50, C3, C4) in 40-60% [24, 25, 37, 46].

From the imaging modalities, the contrast-enhanced CT gives most useful information: the most frequently low-density lesions diffusely or as multiple small nodules in the renal parenchyma or in isolates places of the renal capsule. More rarely, thickening of the renal capsule or of the renal pelvis wall without irregularity of the renal pelvis surface or a diffuse kidney enlargement or a hypodense solitary mass lesion are seen [15, 24, 49].

Histologically TIN with an abundance of IgG4(+) plasma cells, particularly if the ratio IgG4(+) plasma cells/IgG(+) plasma cells is > 40% or if the number

of IgG4(+) plasma cells surpasses 10/HPF from a punch biopsy or exceeds 30/hpf in surgical specimen, is considered a characteristic feature of IgG4-RKD [15, 24, 49]. The parallel detection of storiform fibrosis makes the finding nearly specific for IgG4-RKD and simultaneously facilitates the differentiation from the drug-induced TIN or from TIN in SS. The more rarely detected obliterative phlebitis or eosinophilia support IgG4-RKD, however, their absence does not reject it.

In 2011 simultaneously and independently of each other two proposals for diagnostic criteria for IgG4-RKD were made: the American one [46] promising sensitivity of 100% and specificity of 92% and the Japanese one [55] with values of the same indices 93% and 95%. In 2020 the Japanese proposal was subject to validation on a new clinical material, which determined sensitivity 90.9% and specificity 90% [49]. Up to now, the American criteria are not validated.

In IgG4-RKD a wide differential diagnostics is necessary: ANCA-vasculitides [GPA and Eosinophil Granulomatosis with Polyangitis (EGPA)], Castleman's disease, chronic pyelonephritis, lymphoma, Polyarteritis Nodosa (PN), urinary tract carcinomas, etc. [24, 63].

Recently Li et al. [30] described 19 patients with overlap of ANCA-associated glomerulonephritis (ANCA-GN) and IgG4-RKD and communicate about 28 analogous cases, found in the literature. It is interesting that in the Asian patients IgG4-RKD overlaps predominantly with an ANCA-Microscopic polyangitis (MPA) whereas in European cases – with ANCA-GPA. More impressive, however, is the very overlap of ANCA-GNs and IgG4-RKD as far as according to the consensual postulate [23] the presence of a neutrophilic infiltration and a granuloma (features of ANCA-vasculitides) is in general incompatible with IgG4-RKD. The authors have no pathogenetic explanation of that association. Two hypotheses are expressed: the association between ANCA-GN and IgG4-RKD might be unique subset/entity; possibly, in some circumstance the trigger of ANCA-vasculitis is an underlying IgG4-RKD.

Therapeutic results from the USA are at earliest reported [46]. An extended (on average 14 months) treatment with GC (doses are not shown) leads to a decrease of serum creatinine in 17 from 19 patients (89%) with IgG4-RKD with renal failure. There is no correlation between histologic pattern and response to therapy. Two out of 17 patients (11.7%) had relapse.

The investigations on Japanese material are more multiaspect. In 43 patients with IgG4-RKD with estimated glomerular filtration rate (eGFR) < 60

ml/min the monotherapy with GC of two doses (< 6 mg and > 6 mg/kg/day) leads to increase of eGFR but the degree of improvement shows no significant intergroup difference. In the follow-up average 74 months with maintenance dose GC $\approx$ 5 mg/day the renal function remains without negative progression in 76% of the cases. A conclusion was made that effective induction and maintenance are realizable with more low doses, respectively $\approx$ 5 mg/kg/day and $\approx$ 5 mg/day [48]. In other Japanese patients with IgG4-RKD the treatment with GC 20-50 mg/day (average 36 mg/day), in 5 of them GC together with ISs, until 2-5 weeks normalized or improved CT renal pathology in all patients (100%). After 24 months of maintenance dose 2.5-9.0 mg/day a focal or diffuse renal cortical atrophy in 11/23 patients (48%) was found out. The juxtaposition with various pre-treatment factors reveals that pre-treatment insufficiency (eGFR < 71 ml/min) and serum IgE elevation are predictors for renal cortical atrophy after GC therapy in IgG4-RKD [37].

The overlap of ANCA-GN and IgG4-RKD in 19 Chinese patients with eGFR < 50 ml/min and with increased creatinine in 15 of them was treated by GC (pulse, then p.o. 1,0 mg/kg/day) in combination with cyclophosphamide (CPM) and in 6 patients by plasmaphereses, too. After 16 ± 12 months remission (complete in 6, partial in 9) in 78.9% of ANCA-GN was recorded by means of the BVAS index and an improvement also in 78.9% of IgG4-RKD by the IgG4-RD-RI index (Response Index) [30].

IGG4-RELATED RETROPERITONEAL FIBROSIS

At present, it is accepted that IgG4-related retroperitoneal fibrosis (IgG4-RRPF) encompasses > 75% of the patients with long-ago well-known Ormond's disease. IgG4-RRPF corresponds to the so-called idiopathic form of this disease and the remaining < 25% of the cases represent secondary forms of others pathological conditions (malignancies, infections, radiotherapy, medication use, etc.) [23, 27, 59, 69].

The studies based on smaller materials (5,24,45) show a relative wide scope (7.6-27.0%) of IgG4-RRPF quota amidst all patients with IgG4-RD. Once more the most plausible looks the percentage established in the study of Wallace et al. [62] – 15.8% (78 out of 493). Given the overall population the incidence and prevalence of IgG4-RRPF are low – 0.1-1.3/100,000 population per year and 1.4/100,000 population, respectively [59]. According to all investigations, men are more frequently affected than women – 2.0-3.9:1.0, respectively [7, 31, 45, 62, 69].

Histopathologically IgG4-RRPF represents an inflammatory infiltration of lymphocytes, plasma cells and macrophages interspersed within thick irregular bundles of collagen type 1 fibres. Initially the infiltration dominates fibrosis but subsequently the interrelation reverses. Spreading into the retroperitoneum, the fibrous tissue involves the ureter(s) with following hydronephrosis (bilateral in 25%, unilateral in 75% of the cases) and eventually renal hypo/atrophy as well as the blood vessels in the retroperitoneum, which is reflected more on the veins (inferior v. cava – lower extremities edema, more rarely – deep vein thrombosis) then on the aorta (periaortitis/aortitis → aneurysm), renal arteries (rarely renovascular hypertension) and iliac arteries (very rarely stenosis) [7, 31, 45, 51, 69, 73]. IgG4-RRPF is accompanied by an analogous process in the lymph nodes (in 25%), liver, kidneys and pancreas (12-15%) [62].

Clinically after a long latent period appears pain (in back, flank, abdomen, testes, upper part of thigh), which is dull, permanent and not modifying with body position. Later oliguria, fatigue, anorexia, weight-loss are reported. Physically with a delay and not always – lower extremities oedema, scrotal swelling, hydrocele or varicocele are found out [24, 31, 57, 58, 69, 73].

Laboratorily in this organ form of IgG4-RD the highest rate (75%) and degree of increase of CRP and ESR and paradoxically – the lowest rate of increase (30-40%) and of the IgG4 serum concentration (average 176 mg/dl) are ascertained as well as of IgE. The serum complement is in referent values. The renal function damage (in 40-60%) is revealed by raising of creatinemia [29, 31, 69].

From all the imaging modalities CT is the most important showing a non-homogenous soft-tissue mass enveloping antero-laterally the abdominal aorta and the ureter(s) with following medial deviation (shifting inside) of the latter as well as and/or v. cava inferior and iliac arteries with their eventual obstruction. MRT could add data about the fibrosis degree, whereas PET/CT – concerning the availability and degree of the mass inflammation. The ultrasound (US) scan can ascertain the changes of the kidneys size and the presence of hydronephrosis, being useful also in the monitoring of therapeutic effect [7, 21, 45, 57, 73].

In the presence of a biopsy specimen the histological examination determining an abundance of storiform fibrosis and obliterative phlebitis and particularly the immunohistological examination revealing > 30 IgG4(+) plasma cells per HPF and still more – the ratio IgG4(+) plasma cells/IgG4(+) plasma cells

> 40%, highly support the diagnosis of IgG4-RRPF [15, 26, 69].

In a differential-diagnostic aspect, one must take into consideration chronic infections (tuberculosis, actinomycosis), malignancies (lymphoma, sarcoma, metastases from carcinomas), drug use (ergotamine, methysergide, dopamine agonists, etanercept, etc.), status post radiotherapy or major abdominal surgeries or trauma, Erdheim-Chester disease [59].

The basic experience in the treatment of IgG4-RRPF is obtained in the patients with idiopathic RPF, from whom are excluded the secondary forms, however, they are not examined purposefully towards IgG4-RRPF [31, 58, 59] and only recently in the study interested in IgG4 [73]. GCs are the first-line therapy – as a monotherapy (in the rare cases without involvement of ureters) or in combination with surgical methods (in the majority of the cases). The initial dose of 0.75-1.0 mg/kg/day over several weeks leads to remission in 75-95% [59] or 58% [73] of patients: normalization of the symptoms, laboratory markers for inflammation and renal function, reduction of the retroperitoneal mass thickness and by simultaneously ureters stenting to removing hydronephrosis. GC dosage gradually, over 6-9 months, is tapered to 5.0-7.0 mg/day. In several cases, ISs (MTX, MFM, CPM, AZA) are included as steroid-sparing agents. The therapeutic effect in both the inductive and maintenance phases and also the problem with relapses are controlled by means of US, CT and MRT [7, 31, 38, 59, 73], rarely by PET [21]. The patients not achieving remission remain with permanent renal injury (often end-stage renal disease) (37).

IGG4-RELATED PULMONARY DISEASE

Joining two anatomically linked nomenclature forms of IgG4-RD (IgG4-related lung disease and IgG4-related pleuritis), three names with one and same meaning [IgG4-lung disease [39, 69], IgG4-related respiratory disease [9, 34, 35] and IgG4-related pulmonary disease [28, 56] are competitively used in the literature. In the present exposition, the third name is preferred.

The hitherto existing data concerning the position of the lungs within the frequency of the organ lesions in IgG4-RD – 14.2% [60], 23.0% [63], 23.4% [66], corresponding to position 8 in the diagram of Miyake et al. [36] – arrange the lungs a little backwards than the majority of the presented IgG4-RD organ forms. According to the most authors the isolated IgG4-RD involvement of the lungs is very rare (< 10%); typi-

cal is the engagement together with others internal organs and lymph nodes. In all investigations males are damaged more often than females, with average ratio of 3:1 [9, 18, 51, 53, 69].

Pathologoanatomically IgG4-RPD emerges with a most large diversity of tissue lesions. In the already classical study of Inoue et al. [18] the lung lesions are generalized into four major subtypes: solitary nodular, round-shaped ground-glass opacities, alveolar interstitial and bronchovascular. Later IgG4(+) inflammatory pseudotumor [68], pleural lesions [42, 61] and hilar lymphadenopathy [34] were added.

On that abundant background the clinical course is paradoxically asymptomatic in 29%, 40%, and even 71% of the patients. In the symptomatic cases, the most frequent is dry cough (53-67%), followed by a low-grade fever (30-40%), exertional dyspnea (15-30%), and chest pain (up to 20%) [3, 5, 18, 35, 42, 62, 69]. Also, in up to 20% were reported symptoms of the upper respiratory tract allergy and asthma and in 5% – an autoimmune condition [18, 53, 62, 69].

Based on laboratory tests inflammatory markers (ESR > CRP), IgG (70%) and IgG4 (88%), RF and ANA (40-60%), IgE (60%) are elevated in a large proportion of patients, but serum complement is lowered (!) in 50% [9, 34, 53, 69].

From all the imaging modalities, CT gives the most valuable information. Very indicative is the descending arrangement of the particular CT-findings according their frequency in IgG4-RPD: ground-glass opacities (92%) > thickening of bronchovascular bundle (69%) > thickening of interlobar septa (54%) > enlarged lymph node (46%) > large (= > 1.0 cm) nodule (23%) > small (= < 1.0 cm) nodule (18%) > honeycombing (15%) > mass (8%) [18].

The pulmonary function tests detect in IgG4-RPD restrictive and obstructive ventilatory dysfunction in 33.3% and 22.2%, respectively, estimated as light degree, as well as a negative correlation between the pulmonary function capacity and the serum concentrations of IgG and IgG4 ($r = -0.661$ and $r = -0.761$, respectively) [9].

In 2009 Tsushima et al. [54] investigated the IgG4 level in a bronchoalveolar lavage fluid and found an oversize difference between the concentrations in IgG4-RPD and pulmonary sarcoidosis. This promising differential diagnostic approach, however, until now is neither validated nor yet tested in other diseases mimicking IgG4-RPD.

On the histological level behind the aforementioned pathological forms of IgG4-RPD an infiltration of lymphocytes and plasma cells, frequently also eosinophils, is seen in various combinations with fibro-

sis, obliterative phlebitis and obliterative arteritis (!) [18, 35, 53, 62, 69]. Concerning fibrosis it is highlighted that it is not of a storiform type but of the active one – with a superiority of the fibroblastic proliferation over the collagen fibres [69]. An important contribution to the diagnosis of IgG4-RPD could be the exceeding of the cut-off for a tissue concentration of IgG4(+) plasma cells: > 50/HPF for a pleura specimen or > 50/HPF for a lung surgical specimen or > 20/HPF for puncture lung biopsy (51,68) as well as the ratio IgG4(+) plasma cells/IgG(+)plasma cells > 40% [15]. It is relevant to remark that these cut-offs are not reached in a part of patients with IgG4-RPD, but they are exceeded in 16-24% of the cases with other conditions mimicking the disease [34, 48, 51, 58].

In support of the identifying IgG4-RPD Matsui et al. [34] propose diagnostic criteria including 5 factors, from which two are extrathoracic – hypocomplementemia and established IgG4-RD involvement of others organs. Based on combinations of confirmed factors one could determine a definite, probable or possible diagnosis of IgG4-RPD. For the present time these criteria are not validated. It is emphasized the necessity of discriminating sarcoidosis, Castleman' disease, ANCA-vasculitides (GPA, MPA, EGPA), SS, carcinoma, unspecific interstitial pneumonia, Rosai-Dorfman disease, etc. [35, 39, 47, 51, 70].

In the treatment of IgG4-RPD several approaches were used. About 1/3 of the patients did not receive therapy and the follow-up did not establish any change in the findings. Nine patients with a nodular or pleural form were treated surgically (partial resection or lobectomy) without a following use of GC and the monitoring did not find out relapses. In the patients with a manifested symptomatics and paraclinical data for an active disease an induction therapy mainly with GC 30-50 mg/day was used and a favorable effect on the symptoms and the imaging findings was reported in 90-100% of the cases. In the course of the tapering GC doses or during maintaining dose (about 5.0 mg/day) relapses emerged with a different frequency, which were overcome by raising GC dose in combination with different DMARDs or RTM. As residual findings after therapy reticular shadows or shrunken pulmonary abnormalities could be seen [35, 39, 47, 53, 68].

IgG4-RELATED VASCULAR DISEASE

IgG4-related vascular disease (IgG4-RVD) also unites two anatomically kindred nomenclature forms of IgG4-RD: IgG4-related aortitis/periaortitis and IgG4-related arteritis/periarteritis [52]. The data con-

cerning its frequency amidst the patients with IgG4-RD are inconsistent: 10-20% [51], 10-30% [37], 22% [45], while in the diagram of Myiabe [36] the aorta takes position 12, whereas the arteries – 25. The males are markedly more often involved than females – 72: 28% [45], 83: 17% [43].

Pathologoanatomically in IgG4-aortitis an inflammation involves predominantly the adventitia and to a lesser extent – the media, whereas in IgG4-periaortitis and periarteritis a perivascular fibroinflammatory tissue with minimal changes of the vessel wall is found. In about 80% of the patients with aortitis, a lesion of large-sized (pulmonary artery, iliac artery) and/or of medium-sized (coronary and carotid arteries) vessels is present, too. In a part of them inflammatory aneurysms develop. Behind all these forms a lymphoplasmacytic infiltration of the vessel wall with predominantly IgG4(+) plasma cells, storiform fibrosis and eventually obliterative phlebitis is present [20, 43, 44, 45].

The local symptomatics of IgG4-RVD is very scant – single cases of a vague pain in the chest, back or abdomen. The contribution of IgG4-RVD to the general IgG4-D symptomatics (fever, weakness, malaise) is inseparable from that of the other concomitant forms of IgG4-RD. On a laboratory level it is worth noting the higher values and higher rate of abnormal results of IgG, IgG4, ESR and CRP in aortitis compared to periaortitis; however, the difference is significant ($p = 0,02$) only in the total IgG [45].

The data from the imaging modalities (CT-angiography, MRT-angiography, FDG-PET/CT) determine as follows: in aortitis or arteritis – a diffuse homogenous vessel wall thickening (> 2.0 mm) and exaggerated 18-FDG-uptake of the same wall in comparison to typical atherosclerosis; in periaortitis and periarteritis – a perivascular soft-tissue mass with a minimal vessel wall involvement. A more rare finding in the aorta/artery is the local lumen dilatation in aneurysms, whereas in periaortitis/periarteritis – the lumen narrowing (stenosis) due to pressure from outside [43, 45].

A histological contribution to diagnosis could be expected in the repair surgeries on the occasion of aneurysm dissection/perforation or carotid endarterectomy, if a lymphoplasmacytic infiltration, damaging more severely adventitia than the media, is found out, and the number of IgG4(+) plasma cells is > 50 /HPF and IgG4(+) plasma cells/IgG(+) plasma cells is $> 50\%$ [15, 43, 45, 52].

IgG4-RVD should be discriminated from giant-cell arteritis, Takayasu arteritis, Behcet disease, Cogan syndrome, relapsing polychondritis, aortic le-

sions in HLA-B27-spondyloarthritides, infectious and non-infectious aortitis, atherosclerosis, sarcoidosis, etc. [43, 61].

Concerning the IgG4-RVD treatment Oyama-Manabe et al. [43], generalizing their own experience and that of other authors, report that GCs in a dose of 0.5-0.6 mg/kg/day are effective within 2-4 weeks, which permits tapering within 2 months. In more extending damage the addition of RTM is admissible [11]. For an evaluation of the effect and also for detecting eventual relapse a multidetector CT and FDG-PET are recommended; the last one in a quantitative variant – for the assessment of the vessel inflammation [43, 71].

More data can be found in the study of Perugini [45]. In the patients with primary IgG4-vasculitides, receiving GC therapy, the addition of RTM yields a CT- and MRT-improvement and a tapering GC within 6 months in all cases. The patients who underwent surgical interventions (successful in all) pre- and postoperatively received RTM. In the secondary vasculitis/periaortitis the patients receiving GC-monotherapy ($n = 7$) achieved favourable clinical and imaging results. In additional 13 patients with refractoriness to or contraindications for GC, the inclusion of RTM caused clinical improvement and tapering of GC within 6 months in all cases and improvement of the imaging findings in 89% of the cases.

CONCLUSION

An old maxim says: “One sees what one knows”. An actual confirmation of this maxim's rightness is IgG4-RD. After creating the concept of IgG4-RD this disorder, imperceptible until recently, incited the creation of more than thousand publications reviewing just single patients to.... hundreds of patients and lead to thorough scientific knowledge about the disease and more favourable therapeutic perspectives for the very patients.

Until now, there are no reports of Bulgarian patients with IgG4-RD. Indirect data about the presence of similar patients are found in the publication of N. Stoilov et al. [7]. The real discerning of this multiform disease requires an awareness of it of both the clinical specialists and the specialists in pathology, imaging modalities and clinical laboratory. If it is distinguished before an advanced tissue fibrosis, IgG4-RD responds well to treatment with glucocorticoids and eventually DMARD, although the maintenance of the therapeutic effect remains a problem.

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