IgG4 associated disease/PGS

Template:PGS **IgG4 associated disease**, (**IgG4-RD**, engl. *IgG4-related disease*, ger. *IgG4-assoziierte Erkrankung*) is a rare systemic inflammatoy disease that usually manifests as a tumorous fribotisation. Even though, historically the disease was describe din the pancreas, numerous organs can be affected, in fact many organs being concurrently affected is not an exception. It appears that many of the previously described diseases are most likely to be organ manifestations of IgG4-RD. Common features of all the disabilities are histopathological changes and an increased level of IgG4 in the serum. On the other hand in some cases the classification of IgG4-associated diseases is based on the analysis of only a small umber of patients, as is it a very rare conditions. Thus, it cannot be ruled out that in reality only in a few cases show IgG4 associated diseases.

History

The first case of the pacreatic disease was supposedly described, in the year 1961 by Sarles and others, as pancreatitis with hypergamaglobulinemia. In 1991 Kawagushi and others described it as sclerotic pancreatitis in patients with primary sclerotic cholangitis. V Yoshida et altri proposed the concept of autoimmune pancreatitis in 1995. Later, a number of of authors demonstrated that patients with autoimmune pancreatitis have an increased level of IgG4. Furthermore, some cases were described by a number of authors a concurrent disability of the pancreas and other organs, but also disability without signs of pancreatic involvement. The histolgical picture of individual affected organs amy differ, but in general they are all similar. All this led to the gradual persuasion that it is a systemic disease which can cause disabilities of various degrees. AT the internationla conference in Boston in 2011, it was decided that autoimmune pancreatitis I. type and all other organ manifestations will be considered as a IgG4 associated disease.[1][2]

The first diseases, which are now considered to be organ manifestations of IgG4- associated disease, were described much earlier. For example Mikulicz syndrome waas described in year 1892, Riedel thyroiditis and Küttner tumor were described in 1896. It is not without interest that for instance Mikulicz syndrome was inaccurately associated with Sjögren syndrome in the 50s. This mistake was only recognised in 2005.[3]

Nomenclature

Despite its relatively short historical development, the nomenclature of IgG4-associated disease has undergone a relatively dramatic development. A number of designations can be found in the English literature:[4]

- IgG4-related autoimmune disease
- IgG4-associated multifocal systemic fibrosis
- IgG4-related systemic disease
- IgG4-related sclerosing disease
- Hyper-IgG4 disease
- IgG4-related disease (IgG4-RD)
- Systemic IgG4 plasmacytic syndrome (SIPS)
- IgG4-related multi-organ lymphoproliferative syndrome (IgG4-MOLPS)
- IgG4-associated disease

IgG4 associated disease is an umbrella term for a number of previously described diseases. It is a disease that is relateively rare, studies show only a few cases. In many of these conditions, IgG4-associated disease is only one of the manifestations (marked with symbol *), for others it is an unusual to extremely rare variant (marked with symbol †) These are mainly the following diseases[4][2]: Template loop detected: Template:Sloupce Upraveno a doplněno podle N. C. Singh, Manual of Pediatric Critical Care[5]

Epidemiology

IgG4 associated disease affects men more than women, and it usually occurs in the sixth decade. The ratio of affected overall is 3,5:1, but organ distribution varies from sex to gender, so for example, head and neck involvement is about as common in men and women. The incidence is reported as 0.28-1.08 / 100,000 population (data from Japan), but the actual incidence is unknown. It is a newly defined disease, it is found that a number of originally separate diseases represent a form of IgG4-associated disease.[2][3]

Clinical picture

Clinically, the disease usually manifests as swelling of the affected organ, usually localized. The course of the disease is usually subacute, with no clear dramatic onset of the disease. Thus, the clinical picture very easily arouses suspicion of cancer, although, for example, night sweats are less common here. In less than 10% of patients, the clinical course may be dramatic. Patients come with marked weight loss, fever, dramatic elevation of acute phase reactants, and other manifestations of a systemic inflammatory response. One organ may be affected, but several organs may be affected simultaneously or sequentially. The following organs are usually affected:[2][3] Template loop detected: Template:Sloupce Upraveno a doplněno podle N. C. Singh, Manual of Pediatric Critical Care[5]

In some patients, the symptoms overlap with allergic manifestations; Because allergies are relatively common, it is uncertain whether this is an accidental coincidence. On the other hand, probably up to half of patients have a history of allergies, asthma, eczema, chronic sinusitis or mild eosinophilia.[2][3]

Spontaneous improvement may occur in a small number of patients, but in most patients the course of the disease is rather slow with a worsening of the condition..[3]

Pathology

Histological image

The histopathological triassic of lymphoplasmacytic infiltration, fibrosis, usually storiformly arranged, and obliterative venulitis are classically described. Eosinophilic infiltrate is usually demonstrable, so it is more recently considered as another characteristic feature.[2][3]

Diagnostically significant is the high proportion of IgG4 positive plasma cells in the infiltrate, representing more than 40% of all plasma cells. The diagnostic value of IgG4 immunohistochemical detection is limited by the fact that an increased number is detectable in a number of other disorders. B & nbsp; lymphocytes / plasma cells may aggregate into lymphoid nodules or less frequently form germinal center structures. However, CD4 + T & nbsp; lymphocytes usually predominate in lymphomplasmocyte infiltration. Occasionally, dinuclear plasma cells or Mott cells can be captured. It can be shown that infiltrating populations of plasma cells and T & nbsp; lymphocytes are polyclonal.[2][3]

A relatively characteristic feature is storiform fibrosis. Storiform arrangement is characteristic of some types of tumors, but in the case of inflammatory disorders it is rather an exceptionally occurring histological picture. In the active phase of the disease, fibroblasts and myofibroblasts are scattered in the connective tissue. In the case of a longer-lasting disease, fibroblasts may dominate the histological picture, so that overall the lesion may resemble a mesenchymal tumor. Immunohistochemically, these cells are usually positive for smooth muscle actin and negative for desmin. Storiform arrangement is visible only after some development, in case of sudden flare-up fibrotization is only slightly cellular to acellular, no significant arrangement of ligament is visible.[3]

Obliterating venous involvement (obliterating venulitis, obliterating phlebitis) is a hallmark of IgG4-associated disease. Microscopically, partial or complete obliteration of small and medium caliber veins by an inflammatory infiltrate formed by plasma cells and lymphocytes is evident. There is no fibrin deposition or vascular wall necrosis.[3]

Particularly in the lungs, similar arterial involvement can sometimes be detected. Small and medium arteries are usually affected, but the affected aorta has also been described. When an artery is affected, rapid arterial damage is unusual; it has only been described in larger caliber arteries, including the aorta.[3]

Eosinophil infiltration is demonstrable in almost all cases, sometimes even excessive. In some localities, eosinophilic infiltration is the rule and the clinical unit has this descriptive finding in the name (eosinophilic cholangitis, eosinophilic angiocentric fibrosis, ...).[3][1]

Individual features may be present in a wide range of fibroproductive inflammatory disorders, IgG4-RD is characterised by their combination.[2]

Macrophages tend to be present as part of the inflammatory infiltrate, but if larger areas of infiltrating macrophages are detectable, especially in the case of foam cells or multinucleated giant cells, a diagnosis of IgG4-associated disease becomes highly unlikely. Also, granulomas do not belong to the typical image.[3]

Molecular pathology and pathophysiology

IgG4-associated disease is an inflammatory disease of unclear etiology and not a fully studied pathogenesis. T & nbsp; lymphocytes are thought to play a key role in the pathogenesis. High levels of cytokines stimulating the Th2 response (IL-4, IL-5, IL-13, IFNγ] are evident in lesions.), Fox3-expressing regulatory T cells that produce IL-10 and TGFβ are also evident in lesions. Thus, the environment in the lesion stimulates the Th2 response, i.e., the antibody-directed response, as well as the isotype shift to produce IgE and IgG4.

Ligament production is probably the result of several factors:

- The Th2 response and, in part, regulatory T cells produce the cytokines IL-4, IL-10 and IL-13, which, among other things, cause alternative stimulation of macrophages. Thus stimulated macrophages promote connective tissue production through the production of the pro-fibroproductive cytokines TGF-β and PDGF.
- IL-5 acts chemotactically on eosinophils. Stimulated eosinophils produce TGF-β, PDGF and IL-13. These cytokines activate macrophages, fibroblasts, myofibroblasts. It is the production of cytokines by the eosinophil that appears to be responsible for the storiform arrangement of fibrosis.
- Treg Fox3 + lymphocytes suppress the intensity of ongoing inflammation.
- IL-10, which can be produced by a relatively wide range of cells. Together with IL-4, it leads to the production of IgG4 instead of IgE.

Although the development of the disease takes place under the Th2 response, it is possible that the Th1 response is at the beginning of the disease.

IgG4 antibodies that have only a very low affinity for receptors for Fc fragments of antibodies and a low affinity for C1q, are therefore practically unable to activate complement in the classical way. Interestingly, for example, the switch from IgE to IgG4 plays an important role in allergen tolerance.

IgG4 most likely play the role of an epifenomen without a direct effect on the pathogenesis of the disease. Nevertheless, there are several reasons why it may not be just an epiphenomenon:

- Decreased levels of C3 and C4 can often be observed in patients, in 50-70% of cases with IgG4-associated tubointerstitial nephritis there is even clinically significant hypocomplementemia.
- For type I autoimmune pancreatitis and IgG4-associated tubointerstitial nephritis, co-deposits of IgG4 and C3c can be demonstrated.
- There is a correlation between IgG4 levels and the severity of clinical manifestations, although according to some sources this is not a very strong correlation.
- B cell inhibitor therapy with rituximab usually results in a very rapid remission of the problem.

Therefore, in addition to possible explanations for these phenomena in the context of the assumption that IgG4 production is indeed an epiphenomenon, several hypotheses about the direct involvement of IgG4 in the pathogenesis have been proposed:

- A small proportion of plasma cells may produce IgG1, which is able to induce inflammation.
- To a large extent, hypothetical tissue deposits containing IgG4 can activate complement in an alternative and lectin way and thus stimulate inflammation. The formation of IgG4 deposits is supported by the special behavior of IgG4. The chains are not linked by disulfide bridges, as would be appropriate for antibodies, but are linked only non-covalently. This allows for a so-called Fab arm exchange, in which an IgG4 molecule becomes monovalent with respect to a particular epitope. Such antibodies could, under certain circumstances, lead to the formation of relatively bulky immunocomplexes.

The intrinsic antigenic specificity of IgG4 antibodies may vary, and antibodies characteristic of IgG4-associated disease have not been shown to develop. For example, in patients with autoimmune pancreatitis type I, antibodies against a number of autoantigens have been shown. In this context, a possible link between autoimmune pancreatitis and infection has been identified *H. pylori*.[3]

Diagnostics

There are several diagnostic criteria to diagnose IgG4-RD. These include clinical behavior, laboratory and histopathological findings. Organ-specific diagnostic criteria are available for some organs.

Findings suspicious for IgG4 associated disease

Umehara et al. published in 2012 a list of clinical and laboratory conditions that increase the suspicion of IgG4-associated disease:[4]

- *'clinical picture highly suspicious of IgG4-associated disease'*
  - symmetrical swelling of the lacrimal, parotid or submandibular glands
  - autoimmune pancreatitis
  - retroperitoneal fibrosis
  - suspected Castleman's disease
- *'laboratory finding highly suspicious of IgG4-associated disease'*
  - serum IgG4 higher than 1.35 g / l
  - the ratio of IgG4 + / IgG + cells in the biopsy is higher than 40%
- *'clinical picture suspected of IgG4-associated disease'*
  - unilateral swelling of at least one lacrimal, parotid or submandibular gland
  - orbital pseudotumor
  - sclerosing cholangitis
  - prostatitis
  - hypertrophic pachymeningitis
  - interstitial pneumonia
  - interstitial nephritis
  - thyroiditis / thyroid hypofunction
  - pituitary gland
  - inflammatory aneurysm
- *'laboratory finding suspected of IgG4-associated disease'*
  - hypergammaglobulinemia of unknown origin
  - hypocomplementemia
  - increased IgE or eosinophilia
  - pseudotumorous lesions or swelling of lymph nodes detected by PET with ^{18} F-deoxyglucose

Diagnostic criteria

CCD criteria

In 2011, two Japanese teams led by M. & nbsp; Umehara and K. & nbsp; Okazaki developed diagnostic criteria for the diagnosis of IgG4-associated disease. The General Clinical Diagnostic Criteria (CCD criteria) are as follows:

1. Clinical examination shows characteristic diffuse or localized swelling or mass, one or more organs may be affected.
2. Serum IgG4 concentration exceeds 1.35 g / l.
3. The following histological patterns are captured during histopathological examination:
    1. Severe lymphoplasmacytic infiltrate and fibrosis.
    2. Infiltration of IgG4 by positive plasma cells, both signs are valid at the same time:
    3. * The IgG4 / IgG ratio is greater than 40%.
    4. * There are more than 10 IgG4 positive plasma cells per field of view at maximum magnification.

The diagnosis can be considered definitive if all three points are met. If only the first and third are met, the diagnosis is likely. If the first and second are met, a diagnosis is possible. If a diagnosis cannot be made on the basis of CCD criteria, a diagnosis can be made on the basis of organ-specific diagnostic criteria.[6]

Boston histopathological criteria

In 2011, a symposium on IgG4-associated disease was held in Boston. One of his outputs was a recommendation for the analysis of the histopathological picture. These criteria are general and do not replace organ-specific criteria (if any). According to the recommendation, the histopathological finding should be classified into one of the following three groups:

1. Histologically highly suggestive of IgG4-related disease (*histologically highly suggestive of IgG4-related disease*).
2. Histologically, IgG4-associated disease is probable (*probable histological features of IgG4-related disease*).
3. Histologically, IgG4-associated disease cannot be confirmed (*insufficient histopathological evidence of IgG4-related disease*).

A histopathological finding can be concluded "histologically strongly indicative of IgG4-associated disease" if at least two (in the case of dacryoadenitis only one of the following) are present:

- dense lymphoplasmic infiltrate,
- fibrosis, usually storiformly arranged,
- obliterative phlebitis.

The number of IgG4 positive plasma cells to meet the conditions is organ-specific, ranging from 10 to 200 cells per HPF. Another necessary proportion of IgG4 positive cells out of all IgG positive cells. The absolute minimum is 40%, but the authors recommend moving the minimum limit to 50%.

The histopathological finding can be concluded "histologically, IgG4-associated disease is likely" unless the full spectrum of histological features of IgG4-associated disease is expressed or the diagnosis is made in an organ where the concept of IgG4-associated disease is uncertain. In general, a finding can be closed in this way in the following cases:

1. IgG4 positive cells are present in sufficient numbers, but only one histopathological feature is detected.
2. Skin and meninx specimen because published data on IgG4 associated disease behavior are limited here.
3. Sample from a fine-needle biopsy. Usually, a thin-needle biopsy will provide a diagnostic picture, but in exceptional cases it may not be completely clear.

In the case of this finding, a correlation of the finding with the clinical picture is necessary to make a diagnosis of IgG4-associated disease, ie in particular the demonstration of an elevated serum IgG4 level or the demonstration of involvement of other organs.

Histopathological findings can be closed "" histologically, IgG4-associated disease cannot be confirmed unless conditions are met for either of the above categories. However, failure to meet the conditions alone does not necessarily rule out a diagnosis of IgG4-associated disease. This may be due to a sampling error, a change due to previous therapy, or a morphological change in progression to the fibrotic phase.[7]

Biochemical testing methods

Elevation of IgG4

Elevation of IgG4 above 1.4 g / l can be demonstrated in 70–80% of patients with autoimmune pancreatitis type I, but even a normal IgG4 value does not rule out a diagnosis. Normal levels appear to be associated with a milder clinical course. IgG4 monitoring is likely to be of limited value, as remission may not be accompanied by a decrease in IgG4 in a relatively large number of cases, and relapse may not be accompanied by an increase in IgG4. Only very limited data suggest that the ratio of IgG4 to total IgG could be a more sensitive figure, with a ratio greater than 8% suspected. In fact, in the case of the manifestation of IgG4-associated disease outside the pancreas, very limited data on the behavior of IgG4 levels are available, the considerations being based on the findings in autoimmune pancreatitis type I & nbsp;[2][3]

However, IgG elevation also occurs in approximately 5% of healthy people, and elevation is relatively common in patients with pancreatobiliary malignancy, inflammatory or infectious disease.[2]

Electrophoresis of serum

In patients, a polyclonal band may appear in the faster migrating γ & nbsp; fraction, leading to the phenomenon of β – γ bridging. It can be shown that this fraction consists of IgG4.[2]

Other changes

Other changes occur quite often, but are not very specific [2]:

- elevation of total IgG
- IgE elevation
- elevation of inflammation markers (FW, CRP)
- Serum ANA is detectable in about half of patients
- rheumatoid factor is detectable in about one-fifth of patients

Decreased levels of complement proteins have also been detected and the presence of a number of antibodies has been demonstrated; the diagnostic significance of these findings is not yet clear.[2]

Screening methods

The radiological picture may show varying degrees of involvement, the distinction from malignancy is usually difficult to impossible.[2] Primary sclerosing cholangitis, where, on the contrary, the finding on cholangiographic examination is characteristic.[8]

Treatment and prognosis

Currently, there are not sufficiently large controlled studies with sufficient follow-up in general for IgG4-RD. IgG4-RD responds well to corticosteroid therapy for a minimum of 3-6 months. The risk of relapse is high. Within 6 months, about a third of patients relapse, during the year more than half of patients and after three years, less than a tenth of patients are without relapse. In the clinical trial phase, therapy is aimed at reducing the number of B & nbsp; lymphocytes rituximab. Rather, only at the level of case reports is there evidence of clinical success with proteasome inhibitor therapies bortezomib.[2]

Overview of some organ specific manifestations

Autoimmune pancreatitis

🔎 *For more information see Autoimmune pancreatitis.*

gG4-associated disease is only "" autoimmune pancreatitis type I "(adult type autoimmune pancreatitis, lymphoplasmocytic sclerosing pancreatitis). Histologically, the disease is characterized by periductal deposition of CD4 positive T cells and IgG4 positive plasma cells, storiform fibrotization and acinar cell atrophy. Further development of the disease usually leads to pancreatic duct stenosis and obliterative fibrosis. Another characteristic and often noticeable feature is obliterative phlebitis.

Autoimmune pancreatitis type I occurs mainly in Asia. It affects older men more often. In addition to the characteristic finding, serum IgG4 elevation is also evident. Other lesions in other organs may appear simultaneously or gradually. In particular, lesions in the lacrimal and salivary glands, lungs, bile ducts, kidneys and retroperitoneum are described, less often in the pituitary gland, thyroid gland and prostate. Disabilities in other localities have also been rarely described. A common feature of lesions is that they all usually respond rapidly to corticosteroid therapy.

The diagnosis is based on the clinical finding, the result of the biochemical examination and the biopsy. There are currently several more or less complicated diagnostic criteria, most notably the International Consensus of Diagnostic Criteria for Autoimmune Pancreatitis and the Clinical Diagnostic Criteria for Type 1 Autoimmune Pancreatitis by the Japan Pancreas Society.

In differential diagnosis, it is crucial to distinguish pancreatic cancer. A therapeutic trial of corticosteroids may be helpful if cancer is unlikely within two weeks. Relapses occur quite often. In addition to corticoids, thiopurinol, mycophenolate and rituximab have been tested in the treatment of resistant forms and in the treatment of relapses.[9][10]

Primary sclerical cholangitis

🔎 *For more information see Primary sclerotic cholangitis, IgG4 associated sclerotic cholangitis.*

IgG4 associated primary sclerotic cholangitis is considered by some authors to be a subtype of primary sclerosing cholangitis, while others point to differences in histological picture, possible radiological abnormalities, differences in clinical behavior, and thus in therapy and prognosis. They then consider IgG4-associated sclerosing cholangitis to be a completely separate entity, the third type of sclerosing cholangitis (in addition to traditional primary and secondary sclerosing cholangitis). The IgG4-associated form is characterized by serum IgG4 elevation

and a rapid response to glucocorticoids. Disability of other organs, especially the pancreas, is relatively common, but virtually any organ can be affected. The cholangiographic finding may be relatively variable, showing signs similar to primary sclerosing cholangitis, cholangiocarcinoma and pancreatic cancer. [8][11]

Diseases of the thyroid gland

🔎 *For more information see Riedel thyroiditis, Chronic (autoimmune) thyroiditis.*

Riedel's goiter is considered a typical manifestation of IgG4-associated disease in the thyroid gland. It is a rare chronic fibroproductive disease with local manifestations of oppression of surrounding structures and systemic disorders of endocrine thyroid function. Because the condition may extend beyond the thyroid gland, the concomitant occurrence of several lesions throughout the body is not uncommon. The disease probably does not even shorten life.[12]

A variant of Hashimoto's thyroiditis, which has been shown to be an IgG4-associated disorder, has been described as a very rare matter. It is not clear from the sources how this lesion was distinguished from Riedel's goiter, which itself may be histopathologically more difficult to distinguish from Hashimoto's thyroiditis.[3]

Links

Virtual slides

Template:Virtuální preparát

Related articles

- IgG4 asociovaná nemoc

References

1.
2.
3.
4.
5. **Cite error: Invalid <ref> tag; no text was provided for refs named `novák01`**
6.
7.
8.
9.
10. {Citace | typ = článek | příjmení1 = Dítě | jméno1 = P. | příjmení2 = Nechutová | jméno2 = H. | příjmení3 = Uvirová | jméno3 = M. | kolektiv = ano | článek = Autoimmune pancreatitis | časopis = Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub | rok = 2014 | číslo = 1 | svazek = 158 | strany = 17-22 | url = http://biomed.papers.upol.cz/pdfs/bio/2014/01/03.pdf | issn = 1213-8118 }}
11.
12.

Literature

-

Kategorie:Patologie Kategorie:Revmatologie