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IgG4-related disease and systemic vasculitis – is there any connection?

Choroba IgG4-zależna a układowe zapalenie naczyń – czy istnieje jakiś związek?

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Słowa kluczowe: choroba IgG4-zależna, układowe zapalenie naczyń, przeciwciała ANCA.

Summary

IgG4-related disease is a relatively new group of diseases of still unknown etiology. It is characterized by elevated serum levels of subclass IgG4 immunoglobulin and by abundant infiltration of IgG4+ plasma cells with typical fibrosis of the affected organs. Elevated concentration of IgG4 may be present in many other conditions associated with chronic inflammation. In recent years, it is noted that this may also apply to patients with systemic vasculitis, in particular antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. The aim of this study is to draw attention to the fact that in some cases, both clinical presentation and histopathological findings in IgG4-related diseases and systemic vasculitis may be similar. The importance of elevated serum IgG4 immunoglobulin in patients with ANCA-associated vasculitis (AAV) is unclear and requires further research.

Streszczenie

Choroby IgG4-zależne to stosunkowo nowa grupa schorzeń o niewyjaśnionej dotychczas etiologii. Charakteryzują się one zwiększonym stężeniem podklasy IgG4 immunoglobulin w surowicy i naciekami tkankowymi z komórek IgG4-dodatnich z typowym włóknieniem zajętych narządów. Zwiększone stężenie IgG4 może występować w wielu innych chorobach przebiegających z przewlekłym stanem zapalnym. W ostatnich latach zwraca się uwagę, że może to dotyczyć również chorych na układowe zapalenia naczyń, szczególnie ANCA-dodatnie. Celem niniejszego opracowania jest chęć zwrócenia uwagi na fakt, iż w niektórych przypadkach zarówno objawy kliniczne, jak i obraz histopatologiczny chorób IgG4-zależnych i układowych zapaleń naczyń mogą być podobne. Znaczenie zwiększonego stężenia IgG4 u chorych z AAV (ANCA-*associated vasculitis*) jest niejasne i wymaga dalszych badań.

Introduction

IgG4-related disease (IgG4-RD) is a relatively new and still not fully understood group of diseases [1, 2]. It is characterised by elevated serum concentrations of the IgG4 subclass of immunoglobulins and typical histopathological features (tissue infiltration by IgG4-positive cells, a cartwheel-like pattern of fibrosis (storiform fibrosis), and obliterative phlebitis) [2–5].

The pathogenesis of the disease remains unclear. Autoimmune and allergic factors are being considered [6, 7]. The G4 subclass (IgG4) is the rarest of the immunoglobulin subclasses. Its structure and properties are unique [8]. It possesses anti-inflammatory activity. The IgG4 subclass is also the only subclass incapable of activating the classic complement pathway. It does, however, display an ability to bind with the Fc fragment of another IgG immunoglobulin. Mice models have demonstrated that subclasses exhibiting no complement activation ability may interact with other IgG antibody subclasses and activate the complement system via the lectin pathway [9]. What is known is that Th2-dependent cytokine activity, such as interleukin 4, 5, 10 and 13 as well as transforming growth factor β (TGF-β), elicits a response in the form of eosinophilia, elevated concentrations of IgG4 and IgE, and progressive fibrosis [8]. The results of studies conducted to date have shown that it is overexpression of Th2 and Treg lymphocytes and their dependent cytokines that plays the main role in the pathogenesis of IgG4-related disease [10–12]. These

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cytokines, primarily interleukin (IL)-10, are responsible for the appearance of allergic symptoms, eosinophilia and elevated concentrations of IgE and IgG4 – typical for IgG4-related disease [13].

IgG4-RD most commonly affects middle-aged and elderly men (mean age – 65 years) [6, 14–16]. Onset of the disease is usually sub-acute with an absence of systemic symptoms, and diagnosis is often incidental. The disease process usually involves multiple organs and leads to progressive organ fibrosis and decreased function. The most commonly affected sites are the pancreas, hepatic bile duct, salivary glands, soft tissues of the orbital cavity, and lymph nodes. Less common sites include the mediastinum, retroperitoneal space, soft tissues, skin, central nervous system, thyroid, respiratory tract, kidneys, prostate, and the mammary gland [2, 6]. Symptoms of the disease may present concurrently or develop metachronously. Over time, usually after a period of several years, the disease progresses to involve new organs, and new symptoms appear. In 2012, Japanese researchers proposed a set of criteria for the diagnosis of IgG4-related diseases (Table I) [6].

IgG4-related disease and vasculitis

Blood vessels of various calibre may also be affected in the course of IgG4-related disease [5, 17, 18]. Clinical similarities between IgG4-related disease and small-vessel vasculitis, particularly ANCA-positive vasculitis (ANCA-associated vasculitis – AAV]) are especially interesting [19]. Symptoms of asthma, involvement of the paranasal sinuses, lungs, kidneys and peripheral eosinophilia are common to both conditions. Publications have described cases of IgG4-related disease with concomitant cutaneous leukocytoclastic vasculitis [20], Henoch-Schönlein purpura [21], or allergic vasculitis with hypocomplementaemia [22].

A noteworthy feature is that some patients with AAV have elevated serum IgG4 concentrations and IgG4+ cell infiltration of affected tissues. Elevated serum IgG4 subclass concentrations are present in most patients diagnosed with IgG4-related disease. It is worth bearing in mind that physiological IgG4 responses may be initiated by repeated exposure to an antigen, and elevated concentrations of IgG4 are also present in chronic inflammation, neoplasms, autoimmune diseases, infections, and vasculitis [23, 24].

Of 158 patients hospitalized at the Mayo Clinic, found to have elevated serum IgG4 subclass concentrations (> 140 mg/dl), only 29 patients (18.4%) fullfiled the criteria for definite or probable IgG4-related disease. At the same time, 9 patients (5.7%) were diagnosed with vasculitis, 5 of whom had granulomatosis with polyangiitis (GPA), 3 had eosinophilic granulomatosis with polyangiitis (EGPA), and 1 patient had polyarteritis nodosa [25]. Similarly, a study conducted by a French centre showed that only 10% of patients with elevated IgG4 concentrations were diagnosed with IgG4-related disease. In this study, 2 of the patients were diagnosed with vasculitis: microscopic polyangiitis (MPA) and cryoglobulinaemia in association with HCV infection [26]. A study by Carruthers et al. determined that the negative predictive value of an elevated IgG4 concentration was 96% and the positive predictive value was 34% [27].

The largest number of reports of elevated serum IgG4 concentrations in patients with AAV concerns patients diagnosed with EGPA [28, 29]. In a comparison of serum IgG4 concentrations in patients with EGPA, GPA and atopic asthma, Vaglio found that 75% of patients with active EGPA had an elevated level of IgG4. Serum IgG4 levels were significantly higher in patients with EGPA compared to patients with GPA or asthma, and IgG4 concentrations among patients with GPA were higher compared to healthy individuals. In patients with EGPA, serum IgG4 concentration correlated with disease activity assessed using the Birmingham Vasculitis Activity Score (BVAS), the number of affected organs and risk factors assessed by the Five Factors Score (FFS); at the same time, IgG4 levels declined during periods of remission [30]. Further research is needed in order to confirm the usefulness of repeated IgG4 determinations in monitoring therapy.

Histopathological features

A number of similarities between IgG4-related disease and AAV are also visible in microscopy images. Abundant inflammatory cell infiltration, focal areas of fibrosis and vascular lesions are characteristic morphological features of both conditions. This is particularly evident in biopsy material from the head and neck ar-

Table I. Clinical diagnostic criteria for IgG4-related disease according to Umehara et al. [6]

1.	Characteristic features of organ involvement in the form of diffuse or nodular enlargement or abnormal organ function
2.	Elevated serum IgG4 concentration (≥ 135 mg/dl)
3.	Histopathological abnormalities: (A) lymphocyte and plasma cell infiltration and fibrosis (B) IgG4+ cell infiltration: > 10 IgG4+ cells per high power field and IgG4+/IgG cell ratio > 40%
IgG4-related disease diagnosis:	
Definite	1 + 2 + 3
Probable	1 + 3
Possible	1 + 2

Table II. Differences between ANCA-positive vasculitis and IgG4-related disease (drawn up according to [19])

Differentiating feature	IgG4-RD	AAV
ANCA antibodies	not found	present
histopathological examination abnormalities	Tissue infiltration by IgG4+ cells, storiform fibrosis, obliterative phlebitis	necrotizing small-vessel vasculitis, granulomas
IgG4+ cell infiltration in affected organs/tissues	> 50 cells per high power field	varied, lower
IgG4+/IgG ratio	> 40%	varied, lower

eas. Necrotizing vasculitis and granulomas, typical features of AAV, are less common in these areas [31].

Researchers from the Mayo Clinic examined biopsy material obtained from patients with GPA and determined that IgG4+ cell infiltration was present in over 18% of these patients. An interesting point is that these infiltrations were only present in bioptates obtained from the upper respiratory tract and orbital tissues (38.1%). They were not found in any other location or in any subject in the control group [32]. From a clinical perspective, this is a very significant observation, indicating that care must be taken when interpreting the results of histopathological examinations and their value in the context of the complete clinical picture. Determining the exact significance of IgG4+ cell infiltrates in the pathogenesis of GPA will require further studies. Some authors have suggested that significantly increased infiltration at these sites is linked to the intensity of inflammation [5]. Lacrimal and salivary gland inflammation leads to the activation of significant numbers of lymph nodules engaged in local IgG4+ cell production. The most important features that differentiate IgG4-related disease from ANCA-positive vasculitis are presented in Table II.

ANCA antibody subclasses

Antineutrophil cytoplasmic antibodies (ANCA) typically belong to the IgG class. Brouwer was the first to demonstrate that both PR3-ANCA and MPO-ANCA, present in a group of patients with AAV, belonged predominantly to the IgG1 and IgG4 subclasses [33]. Many researchers have suggested that a subclass of these antibodies may be involved in the pathogenesis of AAV [34]. Studies have also indicated that ANCA-IgG4 plays an important role in GPA pathogenesis [35–37]. Elevated titres of the MPO-IgG4 subclass in patients with GPA may indicate repeated, chronic stimulation of the immune system [36]. At the same time, many studies have shown that the IgG3 subclass of PR3-ANCA is most closely associated with active disease and renal involvement [34, 35, 38]. However, defining the precise role of the IgG4 subclass of ANCA in the pathogenesis of AAV requires further research.

Conclusions

The association between IgG4-related disease and systemic vasculitis remains unclear. EGPA would appear to be the exception, where overexpression of Th2 lymphocytes and their related cytokines may explain the pronounced IgG4 response. Further studies are required to establish whether elevated IgG4 concentrations in inflammatory vascular disease play a significant role in its pathogenesis or are merely an incidental finding. In clinical practice, the possibility of clinical overlap of these two conditions should be borne in mind.

The authors declare no conflict of interest.

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