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Sjögren's syndrome versus IgG4-related diseases – classification difficulties and treatment progress

Zespół Sjögrena a choroby IgG4-zależne – trudności w klasyfikacji, postępy w leczeniu

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Summary

Sjögren's syndrome (SS) is a chronic autoimmune disorder characterized by lymphocytic infiltration in exocrine glands mainly salivary and lacrimal which affects impairment of their functions. Some patients develop extraglandular symptoms such as chronic fatigue, arthralgia, or lung, renal, central or peripheral nervous system involvement. Recent decades have brought understanding of some pathogenetic mechanisms and offered new therapeutic options by depleting B cells. Furthermore, the American College of Rheumatology proposed a new set of classification criteria based on objective symptoms. IgG4-related diseases are new nosological entities. The clinical course similarities of SS to Mikulicz's disease (a subtype of IgG4-related disease) result in diagnostic difficulties. Typical conditions of them are: an increased IgG4 level and infiltrations of parenchymal organs by plasmatic cells. This review summarizes classification difficulties, pathogenesis and treatment strategies of SS and IgG4-related diseases.

Streszczenie

Zespół Sjögrena (ZS) jest przewlekłą chorobą autoimmunologiczną charakteryzującą się naciekami limfocytarnymi w gruczołach egzokrynnych, głównie ślinowych i łzowych, co doprowadza do upośledzenia ich funkcji. U części chorych występują objawy pozagruczołowe, m.in. przewlekłe zmęczenie, artralgia, zajęcie płuc, nerek, ośrodkowego czy obwodowego układu nerwowego. Ostatnie lata przyniosły zrozumienie niektórych mechanizmów patogenetycznych, dzięki czemu pojawiły się strategie terapeutyczne wpływające na aktywność komórek B. Amerykańskie Towarzystwo Reumatologiczne zaproponowało kryteria klasyfikacyjne ZS oparte na obiektywnych objawach. Choroby IgG4-zależne stanowią nową jednostkę nozologiczną. Trudności diagnostyczne spowodowane są podobieństwami ZS do choroby Mikulicza uznawanej za podtyp choroby IgG4-zależnej. Charakterystycznymi jej cechami jest występowanie zwiększonego stężenia immunoglobulin IgG4 oraz naciekanie narządów miąższowych przez komórki plazmatyczne. Niniejszy artykuł ma na celu przybliżenie klasyfikacji, patogenezy oraz metod terapeutycznych ZS i chorób IgG4-zależnych.

Introduction

Sjögren's syndrome (SS) is a chronic, progressive autoimmune disease first described in the late 19th century. It is characterized by the formation of lymphocytic infiltrations in exocrine glands which leads to the development of dryness of the mouth and eyes. Approximately one-third of patients display systemic symptoms such as fever, weakness, chronic fatigue, and weight loss. Vasculitis, decreased C3 and C4 complement factor levels as well as mixed monoclonal cryoglobulinaemia are indicative of patients at risk of developing lymphomas, primarily B-cell lymphomas. Sjögren's syndrome can occur as a primary disorder (pSS) or secondary to other systemic conditions. The differential diagnosis of SS should always include Mikulicz's disease, a subtype of IgG4-related diseases characterized by simultaneous IgG4+ plasma cell infiltration in the lacrimal, parotid and submandibular glands. Clinically, Mikulicz's disease presents as symmetric enlargement of lacrimal and salivary glands accompanied by mild eye and mouth dryness.

Immunoglobulin (Ig) G4-related diseases (IgG4 RD) were first described at the beginning of the 21st century when an association was observed between develop-

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ment of autoimmune pancreatitis and the presence of IgG4+ cell infiltrations in the pancreas. Immunoglobulin G RD are a heterogeneous group of diseases with a subacute course characterized by IgG4+ cell infiltration of various organs, leading initially to their enlargement and, with time, fibrosis and decreased function of the affected organ.

The purpose of this article is to discuss the classification, pathogenesis and therapy of SS and IgG4-related diseases.

Classification criteria for Sjögren's syndrome

Sjögren's syndrome can be challenging to diagnose, even for experienced rheumatologists, because of the diversity of its clinical symptoms, spanning multiple disciplines, and its often subclinical course. Until recently, diagnosis was based on international criteria developed in 2002 by the American-European Consensus Group (AECG), which included both subjective symptoms and objective tests [1]. In 2012, the American College of Rheumatology (ACR) proposed a new set of criteria based solely on objective tests (Table I). It should be noted that these criteria may be applied to patients manifesting symptoms of SS after the exclusion of hepatitis C virus (HCV) infection, symptoms of acquired immunodeficiency syndrome (AIDS), past head and neck radiotherapy, sarcoidosis, amyloidosis, graft-versus-host disease (GVHD), and IgG4-related disease [2].

Currently recommended ophthalmological assessment involves fluorescein and lissamine green staining and determination of the ocular staining score (OSS); these tests provide more precise confirmation of keratoconjunctivitis sicca than previously possible with the Schirmer test. The patient should not be taking eye drops for glaucoma and should not have undergone any surgical procedures on the cornea or any cosmetic eyelid procedures within the last 5 years [3]. It would appear that the proposed criteria show higher sensitivity (96.3%) and specificity (83%) than earlier criteria. Their shortcomings are that they do not incorporate typical clinical features of SS – dryness of the eyes and mouth – and that treatment may be withheld in patients presenting with these symptoms and, for example, positive for anti-Ro/SSA antibodies. Moreover, the inclusion of ANA and RF testing in the criteria may explain the difficulties encountered when diagnosing patients with other concomitant autoimmune diseases such as systemic lupus erythematosus or rheumatoid arthritis [4].

Table I. Sjögren's syndrome classification criteria proposed by ACR in 2012

Presence of anti-Ro/SS-A and/or anti-La/SS-B antibodies OR rheumatoid factor (RF) and antinuclear antibody (ANA) titre ≥ 1 : 320 in serum
Histopathological analysis of minor salivary glands and a lymphocytic focus score ≥ 1/4 mm^2
Keratoconjunctivitis sicca – OSS (ocular staining score) ≥ 3
The presence of at least 2 of the 3 criteria is indicative of SS

Rasmussen *et al.* conducted a comparison of the AECG and ACR criteria that included a comparison of gene expression profiles. The authors failed to demonstrate superiority of the 2012 criteria over the 2002 criteria and SS patients' gene expression profiles appeared to be similar, regardless of which classification criteria were applied. They concluded that poor understanding of the pathophysiological mechanisms underlying SS is the reason behind the current lack of highly sensitive and specific diagnostic criteria [5].

Classification criteria for IgG4-related diseases

The classification of IgG4-related diseases is based on two main criteria: elevated serum concentration of immunoglobulin IgG4 > 135 mg/dl and symptoms of organ insufficiency involving the salivary and lacrimal glands, the thyroid, pancreas or liver, confirmed by the presence of IgG4(+) plasma cell infiltrations and characteristic storiform, whorled pattern of fibrosis observed in histopathological specimens. Mikulicz's disease is an example of IgG4-related disease [6, 7] that involves symmetric infiltration of the salivary and lacrimal glands leading, initially, to their enlargement. In contrast to SS, sicca symptoms are relatively mild and joint pain is not a feature of the disorder, however: Mikulicz's disease often occurs concomitantly with autoimmune pancreatitis (AIP). Laboratory investigations are negative for rheumatoid factor (RF) and antinuclear antibodies (ANA) and IgG4 concentrations are elevated. Glucocorticoid administration usually results in significant and rapid clinical improvement [8].

Immunoglobulin G4-related diseases may affect any organ. However, besides the salivary and lacrimal glands, they most commonly develop in the pancreas, the liver and bile ducts, the thyroid, and lymph nodes. Autoimmune pancreatitis in the course of IgG4-related disease is usually sub-acute and systemic symptoms are normally absent. Characteristic features include pancreatomegaly and irregular narrowing of the pancreatic duct observed in imaging studies. Early intervention using glucocorticoids usually prevents the development of complications in the form of exocrine pancreatic insufficiency and diabetes. Patients with liver and bile duct involvement most often present with jaundice

Table II. Differences between Sjögren's syndrome and IgG4-related disease

	Sjögren's syndrome	IgG4-related diseases
Age	40–50 years	> 60 years
Sex	women > men	men > women
Affected organs and systems	• exocrine glands, primarily salivary and lacrimal glands • upper and lower airways • musculoskeletal system • kidneys • liver • thyroid • peripheral and central nervous system • cardiovascular system • skin	• pancreas • liver and bile ducts • lymph nodes • thyroid • retroperitoneal space • kidneys • lacrimal and salivary glands (enlarged, but without severe sicca symptoms) • orbital cavity
Immunological investigations	RF ANA > 1 : 320 anti-Ro/SS-A and anti-LA/SS-B antibodies	IgG4 > 135 mg/dl
Histopathological analysis	infiltrations of T-lymphocytes, primarily helper CD4+	infiltrations of lymphocytes and IgG4 + plasma cells (IgG4 > 40%) with typical fibrosis and sclerosis
Treatment	glucocorticoids – their effectiveness has not been confirmed DMARDs – hydroxychloroquine, chloroquine, methotrexate, cyclophosphamide biological drugs – rituximab	respond well to glucocorticoids rituximab

precipitated by infiltration of the bile ducts, acalculous cholecystitis and inflammatory hepatic pseudo-tumor. Immunoglobulin G4 disease involving the thyroid takes the form of Hashimoto's disease or Riedel's goiter with symptoms of thyroid insufficiency whereas IgG4-related lymphadenopathy usually manifests as painless enlargement of multiple lymph nodes, most commonly the mediastinal and subphrenic lymph nodes, and is not normally accompanied by systemic features [9].

Pathogenesis of Sjögren's syndrome

Recent years have seen significant developments in the understanding of the complicated pathogenesis of SS. The traditional concept of the disease was based on the assumption that T lymphocytes, mainly helper (Th) lymphocytes, play a leading role in early SS. B lymphocytes are also activated and produce antibodies directed against soluble nuclear and cytoplasmic components (Ro/SS-A, La/SS-B) and against immunoglobulins (rheumatoid factors), among others; B lymphocytes also predominate in severe infiltrations. T cell infiltrations in exocrine glands are usually benign. Th1/Th2 balance shifts in favour of a Th1 response with Th17-cell expression, the primary source of interleukin 17 (IL-17), which is responsible for inducing local inflammation. This is amplified by interleukin 22 (IL-22), also produced by Th17 cells. Interferon γ (IFN-γ), a Th1 cell cytokine, also plays an important role in the inflammatory process, stimulating the plasminogen activation system. In addition, it would appear that IL-7 and IL-34 as well as angiogenic factors neuropilin 1 and VEGF are also involved in the inflammatory process in salivary glands [10].

In recent years, B lymphocytes have been ascribed an increasingly important role in the pathogenesis of SS; among other things, it was established that peripheral blood of patients with primary SS complicated by lymphoma contains an increased number of B cells belonging to a recently identified CD21-deficient line [11]. The latest studies have also shown elevated levels of B-cell activating factor (BAFF), a member of the tumor necrosis factor (TNF) ligand family produced by B cells and glandular epithelial cells, in the serum of patients with SS and a developing lymphoma [12].

It is believed that there is a certain genetic susceptibility to developing primary SS. The genes responsible regulate B-cell differentiation and activation including, among others, BAFF-encoding genes, whose expression is regulated by type I interferon. Factors responsible for inducing type I IFN production and initiation of the autoimmune reaction may be viruses such as the Epstein-Barr virus (EBV), the hepatitis C virus, enteroviruses or the HTLV-1 (human T lymphotropic virus) [13]. The presence of macrophages and dendritic cells in biopsy specimens obtained from patients with particularly se-

vere glandular infiltration has also been emphasized. Researchers believe that, together with excessive IL-18 and IL-12 expression, they are predictors of lymphoma development [14]. Furthermore, attention is being increasingly drawn to the role of epithelial cells in the development of the inflammatory response – as antigen-presenting cells, they are thought to play an active role in the inflammatory process by producing cytokines and recruiting immunocompetent cells. The term "autoimmune epithelitis" has even been proposed, accurately describing the process taking place in exocrine glands in SS [15].

Attempts are being made to develop an animal model that would explain the chain of reactions taking place in SS – in one such model a pivotal role is ascribed to constant activation of nuclear factor κB (NFκB – nuclear factor κ-light-chain-enhancer of activated B cells) due to a genetic deficit of nuclear protein kinase B. This results in excessive epithelial cell apoptosis irrespective of the presence of autoreactive lymphocytes [16]. Abnormal cholinergic type 3 muscarinic (M3) receptor function may also be a contributive factor in the development of SS. IgG antibodies that block this receptor have been identified in patients with pSS; their presence interferes with the normal functioning of salivary glands [17].

It is also worth mentioning that Mavragani *et al.* recently identified antibodies to 21-hydroxylase, which are a marker of autoimmune adrenal insufficiency, in the sera of almost 20% of patients with pSS. Moreover, the authors ascertained an association between these antibodies and markers of B-lymphocyte activation such as IFN-α, BAFF or IL-21 in minor salivary gland tissues. Although in this study the presence of antibodies was not associated with clinical symptoms of adrenal insufficiency, the results of the Synacthen test, used to assess adrenal reserve, revealed a blunted adrenal response in the form of reduced cortisol output. This study suggests that pSS and autoimmune adrenal insufficiency may coexist, and the mechanism of their development is linked to excessive B-lymphocyte activation [18]. Moreover, the presence of different types of antibodies makes it possible to identify certain subgroups of primary SS and determine the prognosis. There have been frequent reports of primary SS with concurrent anti-citrullinated peptide antibodies (ACPA) that are a predictor of future progression to rheumatoid arthritis or else are an expression of the inflammatory process in the synovial membranes of joints [19, 20]. In addition, the presence of ACPA antibodies may be indicative of non-erosive arthritis [21] whereas IgA antibodies may be associated with dermal vasculitis [22]. Some authors suggest the following profiling for primary Sjögren's syndrome: the presence of Ro/La antibodies is associated with early onset of SS; cryoglobulinemia is indicative of a higher probability of developing lymphoma, and the presence of anti-mitochondrial or anti-smooth muscle antibodies would indicate a greater susceptibility to primary biliary cirrhosis or autoimmune hepatitis, respectively [23].

Another interesting aspect of primary SS is the presence of antinuclear antibodies (ANA) with a centromere pattern of fluorescence (anticentromere antibodies – ACA) that contribute to creating a phenotype intermediate between SS and systemic sclerosis characterized by a low tendency to progress to systemic sclerosis [24], and are responsible for the fibrotic component of organ fibrosis [25]. The combined presence of ACA and third generation ACPA antibodies may prove useful in making a clinical distinction between limited systemic sclerosis and other systemic connective tissue disorders [26].

Pathogenesis of IgG4-related diseases

The pathogenesis of IgG4-related diseases has not been fully elucidated. It is believed that in view of their origins, in essence proliferation of immunoglobulin IgG4-producing plasma cells, they often bear a clinical resemblance to lymphocytic infiltrations [27] and are associated with the presence of neoplasms [28]. Immunoglobulin G4 RD are characterized by elevated cytokine concentrations typical of regulatory T cells (Treg) IL-10 and TGF-β, which may play a significant role in the processes of fibrosis and increased immunoglobulin IgG4 production in affected organs [29]. The role played by periostin is also not without significance; this protein has many diverse functions in both physiological and pathological processes [30]. Production of periostin, encoded by the Postn (GenBank D13664) gene, may be induced by factors such as transforming growth factor β (TGF-β), vitamin K and interleukin 3, 4, 6 or 13, among others. In view of its regulatory function in tissue repair (transient periostin overexpression may be observed in connective tissue several days after an injury) as well as tissue remodeling, particularly through the stimulation of collagen production and distribution and the induction and proliferation of tissue fibroblasts, periostin has significant functions in fields such as osteology, oncology and allergic diseases [31]. Periostin overexpression is observed in IgG4-related diseases and its induction is TGF-β-dependent [32].

Treatment

Treatment of Sjögren's syndrome

The management of SS poses a real challenge for rheumatologists and requires collaboration with specialists from other fields. The underlying cause of the disease remains unknown thus, to date, treatment has

been primarily symptomatic. Treatment of keratoconjunctivitis sicca consists of topical administration of artificial tear substitutes, 0.05% cyclosporine eye drops, systemic drugs that help produce tears through stimulation of the muscarinic M1 and M3 receptors, such as pilocarpine and cevimeline, plugs to block the lacrimal points and cauterization of the lacrimal canaliculi [33, 34]. Recently, topical 0.03% tacrolimus eye drops administered over a period of 3 months have shown significant efficacy in treating symptoms of dry eyes [35].

Non-pharmacological management consists of avoiding air-conditioned environments, cigarette smoke and working on a computer for long periods of time. The basic principles of xerostomia management are maintaining good oral hygiene, keeping the oral mucosa moist with water, avoiding alcohol and smoking cigarettes, using saliva substitutes or systemic muscarinic agonists as well as hydroxychloroquine therapy [33, 34].

Joint symptoms are generally treated with non-steroidal anti-inflammatory drugs, hydroxychloroquine and methotrexate. Calcium channel blockers and angiotensin convertase inhibitors are used to alleviate Raynaud's syndrome. Chronic fatigue syndrome and symptoms of fibromyalgia require treatment with antidepressant medication. Immunosuppressive therapy is reserved for cases with very rapid progression of organ dysfunction. Glucocorticoid and/or cyclophosphamide pulse therapy is administered in cases of central and peripheral nervous system involvement, interstitial lung disease, glomerulonephritis, and vasculitis. Plasmapheresis therapy and intravenous immunoglobulin infusions (IVIG) may be attempted in patients with refractory neuropathy or hematological complications [36].

In the context of recent reports on the significant role of B lymphocytes in the pathogenesis of SS, studies are currently being conducted into the effectiveness of B-cell inhibitors, mainly anti-CD20 monoclonal antibodies and, to a lesser degree, anti-CD22. The results of the studies obtained to date are promising. Rituximab is a chimeric monoclonal antibody directed against the CD20 antigen expressed on the surface of virtually all forms of B lymphocytes, with the exception of plasma cells and early B-cell precursors. The mechanism of B lymphocyte depletion following its administration may involve apoptosis, growth inhibition, complement-mediated lysis and cell-mediated cytotoxicity [37].

Rituximab is effective and safe in patients with active forms of long-standing rheumatoid arthritis [38]. In patients with SS, rituximab appears to be effective in treating chronic fatigue syndrome, vasculitis, arthritis, renal and pulmonary complications as well as peripheral nervous system involvement [39–41]. Rituximab has not been seen to be effective in treating central nervous system complications, a syndrome resembling multiple sclerosis [41]. In addition, rituximab shows limited application in treating sicca symptoms. Pijpe *et al.* demonstrated its effectiveness only in the early stage of the disease, which is associated with the unaltered function of the salivary and lacrimal glands [43]. Gottenberg *et al.* also demonstrated that rituximab's effectiveness depends on the degree of glandular dysfunction and the duration of the disease [44]. In a recently published open study, rituximab was effective in alleviating chronic fatigue and subjective xerostomia, but there was no objective improvement in the function of the salivary and lacrimal glands. B-cell activating factor levels rose as a result of B lymphocyte depletion and dominance of transitional B-cells was observed in addition to an absence of memory B cells. The levels of anti-Ro/SSA and anti-La/SSB antibodies, IFN and antibodies against muscarinic receptors remained unaffected [45]. Rituximab is also used to treat B-cell lymphomas in the course of SS. In addition to alleviating clinical symptoms, treatment leads to a reduction in circulating cryoglobulin and RF levels and normalization of the C4 complement fraction level [46, 47].

Epratuzumab is a monoclonal humanized antibody directed against the transmembrane antigen specific for CD22 B lymphocytes, expressed exclusively on the surface of mature lymphocytes and acting as a negative modulator for the BCR receptor. Compared with rituximab, epratuzumab displays properties that are more immunomodulatory and less cytotoxic and produces a less dramatic depletion of B cells [48]. Study results suggest that it is effective and well tolerated in approximately 50% of patients with SS [49].

Anakinra, an IL-1 receptor antagonist, may also prove to be a new therapeutic option. A *post-hoc* analysis of a double blinded, randomized, placebo-controlled study revealed that the number of medicated patients who achieved a reduction in fatigue was far greater than in the placebo group [50].

Results of studies on the use of mesenchymal stem cells (MSCs) to treat SS are very promising. The effectiveness of this therapeutic option has been demonstrated in the treatment of systemic lupus erythematosus, systemic sclerosis and type 1 diabetes [51–53]. In a study based on an animal model using mice with SS-like disease, MSCs were administered in combination with Freund's adjuvant, with the objective of eradicating autoreactive T lymphocytes in order to substitute them with a normal population of lymphocytes. A reduction in inflammation in the salivary glands was noted, demonstrated by a decrease in TNF-α and TGF-β concentrations. Regeneration of the salivary glands was also observed, evidenced by an increase in FGF (fibroblast growth factor) and EGF (epidermal growth factor) concentrations [54]. Another

study showed that both mice and human subjects had reduced inflammatory infiltration in the salivary glands, increased saliva output, a reduction in disease activity assessed by means of the SSDAI scale (Sjögren's syndrome disease activity index) and a reduction in the level of anti-Ro/SSA antibodies [55].

Treatment of IgG4-related diseases

Treatment of IgG4-related diseases usually consists of glucocorticoid pulse therapy and, in cases of involvement of vital organs unresponsive to steroid therapy, biological therapy using the CD20 receptor inhibitor rituximab [56]. Cutaneous forms of IgG4-related disease are reported to have been treated with the immunomodulating agent thalidomide [57].

Summary

Recent years have provided a fresh understanding of the pathogenesis and treatment of SS [58]. It appears that apoptosis of the epithelial cells of exocrine glands is the initiating factor in this disease, leading to their dysfunction and not, as previously thought, lymphocytic infiltration. The importance of B cells as a significant pathogenic factor in severe cases of SS complicated by the development of lymphoma has also increased. Many cytokines and new cell populations that participate in the autoimmune cascade reaction have been identified, and provide potential therapeutic options. A breakthrough in SS management may have been achieved by the introduction of biological drugs directed against B lymphocytes, particularly rituximab. Stem cell transplantation appears to be another very promising management option. Diagnostic criteria proposed by the ACR in 2012, based entirely on objective tests, should provide a solid foundation for the diagnosis of SS.

In view of its clinical similarities, IgG4-related disease should be considered in the differential diagnosis of SS. This is a relatively new nosological entity with the capacity to impact many vital organs in the body. A detailed histopathological and immunological analysis is essential, as is prompt initiation of targeted treatment in cases with kidney, pancreas or bile duct involvement to avoid irreversible complications.

The authors declare no conflict of interest.

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