Seronegative Rheumatoid Arthritis

Subjects: Rheumatology

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Seronegative rheumatoid arthritis (SNRA) is characterized by the absence of both rheumatoid factor (RF) and antibodies against the cyclic citrullinated protein (ACPA) in serum.

seronegative rheumatoid arthritis | rheumatoid factor | anti-citrullinated protein antibodies

1. Introduction

Rheumatoid arthritis (RA) is an inflammatory disease that primarily affects synovial joints through an autoimmune mechanism. If not treated properly, the disease can lead to bone erosion, joint deformities, and disability. Arthritis can also cause serious extra-articular disorders, including interstitial lung disease, vasculitis, and lymphoma [1][2]. According to the latest 2010 ACR/EULAR criteria [3], the diagnosis is based on a scoring system calculated using symptom duration, the number and type of joints affected, altered acute-phase reactants, and the presence of autoantibodies, such as rheumatoid factor (RF) and/or anti-citrullinated protein antibodies (ACPAs), in serum [4]. Because the presence of RF and ACPA in serum is not necessary for the diagnosis of RA, a substantial number of patients presenting with the typical clinical features of RA in the absence of these autoantibodies can be diagnosed as having RA. The form of RA without RF and/or ACPA is termed seronegative RA (SNRA) [5][6]. Numerous observations have reported that the clinical presentation, course severity, and response to therapy appear to be significantly different between SNRA and seropositive RA (SPRA) [7][8][9]. In recent years, the focus on seronegative forms of RA has increased due to clinicians' sensitivity to the different clinical presentations of RA, as well as the advent of increasingly sophisticated means of both molecular and imaging investigations. In addition, the availability of therapeutic means that can act on different effector functions of immunity has indirectly clarified further distinctive aspects between SNRA and SPRA.

2. Epidemiology

Available epidemiological data have traditionally reported a lower prevalence of SNRA than SPRA, ranging from 20 to 30 percent of total cases of RA [10][11]. However, the incidence of SNRA has been reported to be increased in recent decades [12][13]. Many hypotheses have been advanced to explain this finding. One possible cause is the increasing age of the general population. In fact, late-onset RA occurring in elderly patients is commonly seronegative, suggesting that the dysregulation of inflammation, typical in people of old age, may underlie SNRA [14][15][16]. Another cause is an overall reduction in smoking habits, with cigarette smoking being a strong risk factor for protein citrullination [17]. It is believed that the process of citrullination, by changing the self-nature of joint antigens to non-self-antigens, induces an autoimmune process that leads to the generation of ACPA and causes

the humoral and cellular immune systems to attack the altered joint antigens, resulting in synovitis with tissue damage. Therefore, it is likely that the reduction in smoking increased the incidence ratio between SNRA and the seropositive forms through this immunological mechanism [18]. Other factors reported to explain the increased incidence/prevalence of SNRA are changes in the microbiome, possibly from chronic triggers by gut flora via microbial DNA and pepdidoglycans [19], and some environmental factors, including increased occupational exposure to crystalline free silica [20]. Of course, further studies are needed to clarify whether the upward trend in the incidence/prevalence of SNRA compared with that of SNPA is a finding that can proceed over time and whether there are additional genetic and/or environmental factors causing it, which have yet to be elucidated.

3. Pathogenesis

The first distinction between SNRA and SPRA is their different genetic backgrounds. Although RA is a polygenic disease, some genetic risk factors have been identified for SNRA. Among them, the HLA-B*08/DRB1*03 haplotype is one of the genetic markers most frequently associated with SNRA, while the classical HLA-DRB1*04 and *10 alleles have been shown to be risk factors exclusively for SPRA [21][22]. Non-HLA genes also play a relevant role in determining susceptibility to RA, including mutations in genes coding for Janus kinase (JAK)/signal transducer and activator of transcription (STAT) proteins, which are risk factors for SPRA but not for SNRA [23][24]. A genome-wide association study revealed an association with single-nucleotide polymorphism of non-HLA genes *ANKRD55* [25] and *CLYBL* [26] in SNRA but not in SPRA. It is possible to speculate that mutations in non-HLA genes represent changes in the innate-type immune response through the modulation of the synthesis of cytokines and other soluble factors. Indeed, innate immunity seems to be more prominent in SNRA than in SPRA, while antigen/autoantigen presentation to T lymphocytes by HLA molecules represents a key element of adaptive immunity that is more typical of SPRA pathogenesis.

The study of the expression of miRNA is a new exciting field of research aiming to identify biomarkers for differentiating SNRA from SPRA. In this regard, it was recently reported that the miRNAs has-miR-362-5p and has-miR-708-3p were upregulated in SNRA but not in SPRA. Other miRNAs were found to be downregulated differently in the two forms of RA, including the mRNAs expressed exclusively in SPRA and others common to both forms [27][28]. **Table 1** summarizes the different genetic backgrounds and miRNA expressions between SNRA and SPRA.

Table 1. Susceptibility to SNRA and SPRA is favored by the presence of HLA and non-HLA genetic factors and miRNA expression.

Feature	SNRA	SPRA	References
HLA-B*08/DRB1*03	High	Low	[21]
HLA-DRB1*04/*10	No	High	[29]
SNP *ANKRD55*	High	No	[25]
SNP *CLYBL*	High	No	[26]

Feature	SNRA	SPRA	References
has-miR-362-5p	High	Low	[27]
has-miR-708-3p	High	Low	[28]
has-miR-24	High	High	[30]
has-miR-125a	High	High	[30]
has-miR-22	Low	High	[30]
has-miR-361-5p	Low	High	[30]
has-miR-233-3p	Low	High	[30]

Some studies were conducted to determine the differences between SPRA and SNRA at the cellular level. The synovial histological score for CD4+ T cells, CD68+ cells in the lining layer, and sublining CD3+ and vessel CD31+ positive cells was less abundant in undifferentiated seronegative arthritis than in differentiated SPRA [28]. It has also been reported that synovium-infiltrating monocytes and macrophages predominate in SNRA [21]. In an attempt to identify biomarkers that can differentiate SNRA from psoriatic arthritis (PsA) because they share some clinical features, a study was conducted that analyzed the synovial histopathology of the two diseases. It was reported that plasma cells predominate in the synovium of SNRA, while mast cells predominate in PsA [31].

An immunohistochemical analysis of the synovium also revealed a higher percentage of tissue-resident dendritic cells and a reduced expression of the PD-1 inhibitory receptor on T cells in SNRA compared with its seropositive counterpart [32]. Therefore, the finding that the immune checkpoint inhibitor PD-1 can induce SNRA in the course of cancer therapy is of particular interest [33]. **Table 2** shows the inflammatory cells detected in the synovial membrane during SNRA and SPRA.

Table 2. Immunological features of SNRA and SPRA.

Cell Type	SNRA	SPRA	References
Synovial lining CD68+ cells	Rare	Frequent	[28]
Synovial CD4+ T cells	Rare	Frequent	[28]
Synovial vessel CD31+ cells	Rare	Frequent	[28]
Synovial monocytes	Frequent	Rare	[21]
Synovial macrophages	Frequent	Rare	[21]
Plasma cells	Frequent	Rare	[32]
PD-1+ T cells	Rare	Frequent	[33]

Interestingly, SNRA occurrence has been reported during asthma therapy with anti-IL4/IL-13 biologics with the activation of the IL-23-IL-17 axis, suggesting a protective role of T helper-2 (TH-2) cells in the disease [34]. This evidence further supports the idea that SNRA is a form of RA that diverges substantially from SPRA and suggests a similarity of SNRA with SpA, which depends primarily on IL-17 [5][35][36]. Several observations point out that SNRA has a more variable outcome, generally associated with a better prognosis than SPRA [37][38]. It is interesting to note the reported association between SNRA with NLRP3 inflammasome activation. In this regard, studies have demonstrated a role for interleukin-beta (IL1β), a key component of the inflammasome, in the pathogenesis of SNRA [39]. The pathogenetic relationship between SNRA and IL-1β may explain the favorable response to the interleukin-1 receptor antagonist (IL-1ra), as observed in some patients with SNRA, and the minor response to JAK inhibitor (JAKi) therapy of SNRA compared with SPRA, as reported in some studies [40][41][42]. This can be related to the fact that IL-1 does not depend on the JAK/STAT transduction pathway. As is well known, the activation of the NLRP3 inflammasome by monosodium urate crystals with the release of IL-1β plays a major role in the initiation of gout flare [43]. Interestingly, elevated uric acid levels and crystal deposition are occasionally observed in SNRA but not in SPRA, indirectly suggesting an at least partially autoinflammatory nature of SNRA [43]. Although it is not easy to give an explanation for these observations, they suggest a possible pathogenetic link between SNRA and crystal deposition arthritis. Similarly, an autoinflammatory nature has also been proposed for spondyloarthritis (SpA) [44]. To elucidate the possible autoinflammatory component of SNRA, further studies using methods to study the inflammasome and the genetic substrate of this form of RA are needed. In addition, it should be noted that the study of synovial histology is providing very promising results due to the precise characterization of the cells that infiltrate this tissue. Using the methods of histochemistry and flow cytometry, many research groups are trying to identify new biomarkers that can differentiate SNRA from SPRA. Although synovial biopsy is an invasive procedure, it cannot be ruled out that, in the near future, the results obtained may allow for the development of serologic tests that allow for differential diagnosis through simpler diagnostic tests. Pathogenetic characterization, of course, not only has a scientific or diagnostic purpose but also appears essential for the setting of targeted therapies and the possible realization of the so-called personalized therapy tailored to the individual.

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