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Role of autoantibody testing

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A B S T R A C T

Autoantibodies are the serological hallmark of autoimmune disease. Though their pathogenic role is debatable, they play an important role in the management of a patient with rheumatic disease. However, due to their presence in the general population as well as in multiple autoimmune diseases, the presence of an autoantibody alone does not make a diagnosis; the result has to be interpreted along with clinical findings. Similarly, the absence of autoantibody does not exclude a disease.

The common autoantibodies used in clinical practice include rheumatoid factor, anti-CCP antibodies, antinuclear antibodies (ANAs), anti-neutrophil cytoplasmic antibodies (ANCA) and anti-phospholipid antibodies. Once an autoantibody to a broad antigen is detected in a patient, sub-specificity analysis can improve the utility of the antibody. Autoantibodies are detected in the serum using different assays and results of which can vary; thus, it is important for a clinician to know the method used, its sensitivity and specificity to help in the proper interpretation of the laboratory results. This review will address these issues.

Introduction

During the development of lymphocytes in the primary lymphoid organs, the body tries to avoid generation of cells directed against self-antigens; however, the deletion process is not perfect, and a small frequency of self-reactive T and B lymphocytes escape to the periphery. In the periphery, they are

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kept under check by different mechanisms involved in tolerance induction. However, in autoimmune disease due to the failure of these regulatory mechanisms or to an increased load of autoantigens, there is a generation of a significant amount of autoantibodies. The pathological significance of autoantibodies in the causation of disease is limited, but they serve as good serological markers of autoimmunity.

Autoantibodies are useful in diagnosis, prognosis and follow-up of patients with rheumatic disease. However, as is true for any laboratory test, the interpretation of the test is dependent on the clinical situation (pre-test probability), the characteristics of the test (sensitivity, specificity and the likelihood ratios) and the reason for doing the test (confirmation or exclusion of a diagnosis). Autoantibodies can be directed against any component of a cell, that is, nuclear, cytoplasmic or membrane. In addition, antibodies against cytokines, hormones, coagulation proteins, phospholipids, etc. are also known.

Most autoantibodies for clinical usage are detected in the serum, but they can be detected in the cerebrospinal fluid and other body fluids. The various tests used for their detection include indirect immunofluorescence assay (IIF), enzyme-linked immunosorbent assay (ELISA), nephelometry and immunoblotting. In recent years, newer techniques such as bead array and chip array are being explored for the ease of automation and a high throughput.

For each test, kits from various companies are available; however, the results are usually not comparable due to differences in the various reagents used. Though there has been an attempt to standardize kits and express results in international units, it has not been possible for all antibodies. Kits certified by a regulatory body such as Food and Drug Administration (FDA) or European Medicines Agency (EMA) should be used.

The autoantibody testing is different from other laboratory tests because of the presence of multitude of antibodies in one disease, the same antibody in many diseases, occurrence prior to the onset of symptoms and fluctuation in levels during the course of a disease. Autoantibodies are also found in healthy individuals, and their prevalence increases with age especially so in the elderly population, which further makes their interpretation difficult. Thus, their interpretation requires training of physicians so that they are used in the right clinical context.

In this review, commonly used autoantibodies and their clinical significance are discussed.

Rheumatoid factor: Rheumatoid factor (RF) is an autoantibody directed against aggregated immunoglobulin G (IgG). They are produced as a result of polyclonal B-cell activation as well as in response to the modified antigen. Though all subtypes of RF are generated, we usually test for IgM RF. IgG and IgA are present in a proportion of patients with RF. RF is present in many conditions besides RA (Table 1).

The presence of RF in a patient with arthritis increases the probability of a diagnosis of rheumatoid arthritis (RA). In a patient with RA, it increases the risk of the development of erosions, extra-articular features and poor outcome. In RA, the presence of RF also increases response rate to B-cell depletion therapy.

In addition to RA, RF is present in many autoimmune diseases such as Sjögren's syndrome (SS), systemic lupus erythematosus (SLE), juvenile idiopathic arthritis, all of which may present with polyarthritis. Patients with chronic infections such as subacute endocarditis, tuberculosis (TB) and leprosy

Table 1
Prevalence of RF in different clinical situation.

Disease	Prevalence	Disease	Prevalence
Rheumatoid arthritis	60–70	**Chronic infections**	
Early undifferentiated arthritis	45–55	Endocarditis	15–20
Juvenile idiopathic arthritis	10–12	Hepatitis B/C	15–40
Other autoimmune diseases		Leprosy	10–50
SLE	15–30	Tuberculosis	10–20
Sjögren's syndrome	75–85		
Systemic sclerosis	20–30		
Inflammatory myositis	5–10		
Interstitial lung disease	10–40	Healthy control	5–20[a]

[a] Elderly persons.