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RHEUMATOLOGIC DISEASES

Susan P. Bruce and Terry L. Schwinghammer

OBJECTIVES

After completing this chapter, the reader should be able to

- Describe the physiologic basis for rheumatologic laboratory tests and the pathophysiologic processes that result in abnormal test results
- Understand the appropriate clinical applications for laboratory tests used to diagnose or assess the activity of select rheumatologic diseases
- Interpret the results of laboratory tests used to diagnose or manage common rheumatologic diseases
- Use the results of rheumatologic laboratory tests to make decisions about the effectiveness of pharmacotherapy
- Employ laboratory tests to identify and prevent adverse reactions to drugs used to treat rheumatologic diseases

The diagnosis and management of most rheumatologic diseases depend primarily on patient medical history, symptoms, and physical examination findings. A variety of laboratory tests are used to assist in the diagnosis of rheumatologic disorders, but many are nonspecific tests that are not pathognomonic for any single disease. However, the results of some specific laboratory tests may be essential for confirming the diagnosis of some diseases. Consequently, laboratory tests are important diagnostic tools when used in concert with the medical history and other subjective and objective findings. Some laboratory test results are also used to assess disease severity and to monitor the beneficial and adverse effects of pharmacotherapy.

The diagnostic utility of a laboratory test depends on its sensitivity, specificity, and predictive value (Chapter 1). Tests that are highly sensitive and specific for certain rheumatologic diseases often have low predictive values because the prevalence of the suspected rheumatologic disease is low. The most important determinant of a laboratory test's diagnostic usefulness is the pretest probability of disease, or a clinician's estimated likelihood that a certain disease is present based on history and clinical findings. As the number of disease-specific signs and symptoms increases and approaches diagnostic confirmation, the pretest probability also increases.

After briefly reviewing pertinent physiology of immunoglobulins, this chapter discusses various tests used to diagnose and assess rheumatologic diseases, followed by interpretation of these test results in common rheumatologic disorders. Tests used to monitor antirheumatologic pharmacotherapy are also described.

STRUCTURE AND PHYSIOLOGY OF IMMUNOGLOBULINS

Many rheumatologic laboratory tests involve detection of immunoglobulins (antibodies) that are directed against normal cellular components. The structure and functions of immunoglobulins are reviewed briefly here to facilitate understanding of these tests.

When the immune system is challenged by a foreign substance (antigen), activated B lymphocytes differentiate into immunoglobulin-producing plasma cells. Immunoglobulins are Y-shaped proteins with an identical antigen-binding site (called *Fab* or *fraction antigen-binding*) on each arm of the Y (**Figure 19-1**). Each arm is composed of a light (L) amino acid chain covalently linked to a heavy (H) amino acid chain. The terms *light* and *heavy* refer to the number of amino acids in each chain. Because the heavy chain has more amino acids than the light chain, it is longer and has a higher molecular weight.

Both types of chains have a variable region (V_L and V_H) and a constant region (C_L and C_H). The variable regions contain the antigen-binding sites and vary in amino acid sequence. The sequences differ to allow immunoglobulins to recognize and bind specifically to thousands of different antigens. Within the variable regions, there are four framework regions and three complementarity-determining regions; together these make up the antigen-binding pocket. The constant region of the light chain (C_L) is a single section. Immunoglobulins that have identical constant regions in their heavy chains (e.g., C_H1, C_H2, and C_H3) are of the same class.

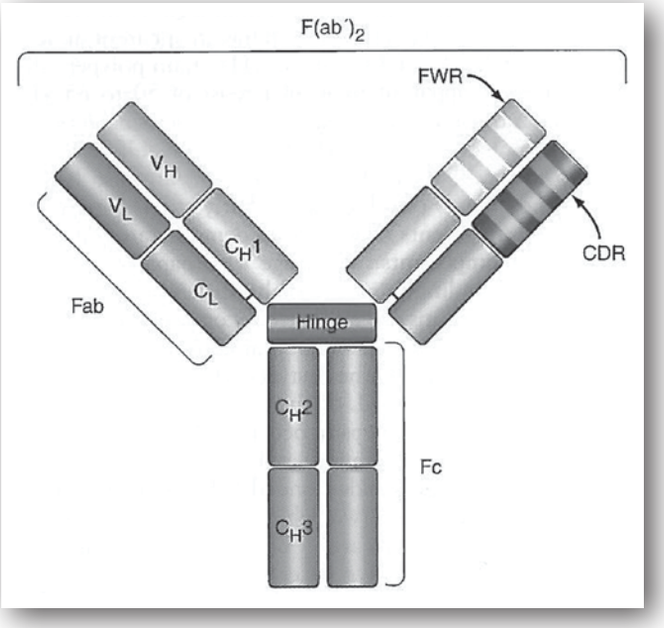

FIGURE 19-1. Schematic of the antibody molecule. (Reproduced, with permission, from Orduno NM, Grimaldi C, Diamond B. B cells. In: Firestein GS, Budd RC, Gabriel S et al., eds. Kelley's textbook of rheumatology. 9th ed. Philadelphia: Saunders Elsevier; 2013;192.)

The five classes of immunoglobulins are IgA, IgD, IgE, IgG, and IgM. Depending on the immunoglobulin, the constant region of the heavy chain has either three domains and a hinge region (IgA, IgD, and IgG) that promotes flexibility, or four domains without a hinge region (IgE and IgM). Thus, the immunoglobulin's heavy chain determines its class (alpha heavy chains, IgA; delta heavy chains, IgD; epsilon heavy chains, IgE; gamma heavy chains, IgG; and mu heavy chains, IgM). Tests are available to measure the serum concentrations of the general types of immunoglobulins as well as immunoglobulins directed against specific antigens (viruses, other infectious agents, other allergens).

In Figure 19-1, the second and third domains (C_H2 and C_H3) of the heavy chain are part of the Fc (fraction crystallizable) portion of the immunoglobulin. This portion has two important functions: (1) activation of the complement cascade (discussed later); and (2) binding of immunoglobulins (which react with and bind antigen) to cell surface receptors of effector cells such as monocytes, macrophages, neutrophils, and natural killer cells.[1]

TESTS TO DIAGNOSE AND ASSESS RHEUMATOLOGIC DISEASES

Blood tests that are relatively specific for certain rheumatologic diseases include rheumatoid factors (RFs), anticitrullinated protein antibodies (ACPAs), antinuclear antibodies (ANAs), antineutrophil cytoplasmic antibodies (ANCAs), and complement. Nonspecific blood and other types of tests include erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), analysis of synovial fluid, and others. Where applicable, the sections that follow discuss quantitative assay results (where normal values are reported as a range of concentrations), qualitative assay results (where assay results are reported as only positive or negative), and their use in common rheumatologic and nonrheumatologic diseases.

Anticitrullinated Protein Antibodies

Citrullination is the process by which susceptible genes exposed to environmental factors undergo an abnormal change. As a result, citrullinated proteins become antigens and lead to the formation of autoantibodies. ACPAs bind to the nonstandard amino acid citrulline that is formed from removal of amino groups from arginine. Nonstandard amino acids are generally not found in proteins and often occur as intermediates in the metabolic pathways of standard amino acids. In the joints of rheumatoid arthritis (RA) patients, proteins may be transformed to citrulline during the process that leads to joint inflammation. The creation of citrullinated proteins is not specific to RA. However, the resulting formation of ACPAs is unique to RA. When these antibodies are present, there is a 90–95% likelihood that the patient has RA. The combination of both positive RF and positive ACPA has 99.5% specificity for RA.

The ACPA test is most useful in helping to identify the etiology of inflammatory arthritis in patients with negative rheumatoid factor (RF) titers. ACPAs are detected in about 50–60% of patients with early RA, usually after three to six months of symptoms.[3] It has been theorized that citrulline antibodies represent the earlier stages of RA in this situation. The presence of ACPAs have also been associated with more erosive forms of RA. The presence of ACPAs is considered one of the clinical features of RA that are associated with a worse long-term prognosis. Therefore, ACPA-positive patients with moderate or high disease activity should receive aggressive treatment early in the course of RA.

Quantitative and Qualitative Assay Results

Normal values: <20 EU/mL (assay dependent)

Quantitative ACPAs are tested by enzyme-linked immunosorbent assay (ELISA) and are reported in ELISA units (EU). The relationship between these values and qualitative results are generally reported as the following:

- <20 EU: negative
- 20–39 EU: weakly positive
- 40–59 EU: moderately positive
- >60 EU: strongly positive

Rheumatoid Factor

Rheumatoid factors (RFs) are immunoglobulins (predominantly IgM but may also be IgG or IgA) that are abnormally directed against the Fc portion of IgG. These immunoglobulins do not recognize the IgG as being "self." Therefore, the presence of RFs in the blood indicates an autoimmune process. The RF measured in most laboratories is IgM-anti-IgG (an IgM antibody that specifically binds IgG). Like all IgM antibodies, IgM RF is composed of five subunits whose Fc portions