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The management of the patient with unexpected autoantibody positivity

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Abstract

Different autoantibodies are often measured simultaneously; this typically occurs when using indirect immunofluorescence on tissue sections or multiplex detection systems and may generate clinically "unexpected" positivities (i.e., without any relation to the disease under investigation). Their number is expected to increase with the development of microarray systems in autoantibody assays. In general, when examining patients with such unexpected findings, it is necessary to take into account that: a) autoantibody positivities are much more frequent than autoimmune diseases; b) the positive predictive value of an autoantibody positivity depends upon the diagnostic accuracy of the test and disease prevalence; c) autoantibodies may be risk factors for autoimmune disease or may also have a pathogenetic role by themselves.

In this article we will highlight the possible problems raised by some relatively common situations, related to anti-nuclear, anti-thyroid, anti-phospholipid and anti-tissue transglutaminase autoantibodies. The need for specific strategies is outlined.

Keywords: Autoimmune disease; Autoantibodies; Anti-nuclear antibodies; Anti-TPO antibodies; Anti-phospholipid antibodies; Celiac disease

Contents

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1. Introduction

The detection of specific autoantibodies in the serum is an important tool in diagnosing autoimmune diseases; however, diagnostic accuracy is extremely variable, depending on different diseases or different autoantigen/autoantibody systems. Often specific autoantibodies are detectable in the serum years before the onset of clinical disease; on the other hand, autoantibody positivity may be transient, that is, the autoantibodies disappear without any evidence of clinical disease. In addition to autoantibodies of relatively selective specificity, there are also natural autoantibodies, whose specificity is broader and serum concentration generally lower; although their pathophysiological meaning is not fully understood, it is known that they have a number of possible physiological functions, such as facilitating the clearance of catabolic products from the organism.

On the basis of these considerations, it is apparent that autoantibody positivity does not necessarily lead to the diagnosis of autoimmune disease. This is of crucial importance when deciding how to treat the patient exhibiting "unexpected" autoantibody positivity.

What should we define as "unexpected" autoantibody positivity? Clearly, when search for serum autoantibodies derives from definite clinical suspect [as an example, the presence of two clinical criteria for systemic lupus erythematosus (SLE)], positivity is "expected" and definitely suggests a diagnosis and indicates a clinical strategy. Conversely, when search for autoantibodies does not arise from definite clinical suspect, but from screening or case-finding procedures, autoantibody positivity may be defined as "unexpected" and the clinical management of the patient has to be defined. However, totally "unexpected" positivities (not related to any screening or case-finding procedures) may arise for methodological reasons. Combined tissue sections (liver, kidney, stomach) have long been used for the detection of a number of autoantibodies by means of indirect immunofluorescence (IIF). This may allow for the detection of autoantibody specificities (e.g. nuclear, reticulin) which are not related to the original clinical problem. It is expected that in the next few years the wider availability of microarray systems which permit the simultaneous detection of a variety of autoantibodies [1,2] will result in a major increase of "unexpected" positivities. This, however, raises a number of ethical questions, but more importantly, leads to a careful study of clinical management. We will deal with the latter point. Two main factors affect the diagnostic value of specific autoantibody assays: diagnostic accuracy and the prevalence of related disease. Obviously, serum concentration, titres and isotype are usually important. Some specific situations will be focused on.

2. The case of anti-nuclear antibodies

Anti-nuclear antibodies (ANA) are a major tool for the diagnosis of systemic autoimmune diseases, with special reference to SLE [3]. They are assayed by means of indirect immunofluorescence on HEp2 cells, or also by screening immunometric methods [4,5]. In our institute, ANA testing represents a very consistent proportion (about 30%) of the overall autoantibody determinations (Fig. 1). However, if we consider the relative prevalence of the different autoimmune diseases, both systemic and organ-specific, SLE accounts for about 0.2% of the total, Sjögren's syndrome for about 2%, and other autoimmune diseases in which ANA may occur (mixed connective tissue disease, systemic sclerosis, autoimmune hepatitis) taken together account for less than 0.5% (Fig. 2). This means that in many instances ANA are investigated on the basis of limited clinical data; this may be partly due to the complexity and elusiveness of the clinical presentation in the wide spectrum of autoimmune connective tissue diseases.

On the other hand, a relatively high proportion of apparently healthy individuals has positive ANA (as many as 5% at 1:160 dilution, more than twice at 1:80) [6].

As a consequence, the majority of results of current ANA determination are expected to be negative, but more importantly, the likelihood of false-positive results is very high. In fact, when considering patients selected for having only one clinical criterion for SLE diagnosis, in whom about 1% SLE prevalence is expected, the negative predictive value of ANA has been estimated to

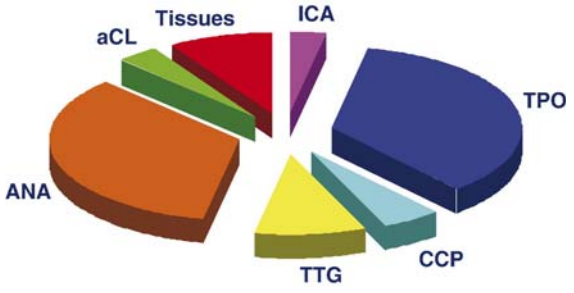

Fig. 1. Relative frequencies of some commonly used autoantibody assays (TPO, anti-thyroid peroxidase; ANA, anti-nuclear antibodies; aCL, anti-cardiolipin antibodies; ICA, anti-islet cell antibodies; CCP, anti-cyclic citrullinated peptide; TTG, anti-tissue transglutaminase antibodies; tissues, assays on liver/kidney/stomach tissue sections). Data from assays performed in 3 reference laboratories of Liguria, Italy, in the first 6 months of 2005.