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LETTER TO THE EDITOR

A proposed model for effective collaboration between rheumatologists and clinical pathologists for the diagnosis of autoimmune rheumatic diseases

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Tests for detecting autoantibodies are very useful in diagnosing and monitoring autoimmune rheumatic diseases (ARD). However, the continual discovery of new specific autoantibodies and the great advances in laboratory technology have given rise in recent years to the introduction of new tests and new diagnostic methods to the point that the clinician may find himself in difficulty as to which tests should be requested in a given context and how the results obtained should be interpreted.

In fact, if we consider that more than 100 autoantibodies have been described in cases of systemic lupus erythematosus [1] alone, and that some of these may appear in asymptomatic subjects and may precede the appearance of clinical manifestations by years [2, 3], the ability to differentiate among the results of various methods, which often present differing characteristics of sensitivity and specificity, may cause serious difficulties in the interpretation of test results, certainly on the part of general practitioners but also at times for the consultant rheumatologist [4].

In addition, the ever-increasing number of requests for autoantibody tests, especially by general practitioners, must be considered.

Another major change is that the serological diagnosis of ARD takes place more and more often in centralized laboratory hospitals and less often in university clinics where historically there was greater competence in test interpretation.

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One aid to the clinician may come from the many guidelines available today that not only provide a flow chart of the tests required to support the diagnosis and to calculate the prognosis, but are useful also toward the end of determining a reasoned and economical use of serological tests [5–11]. Unfortunately, despite the abundance of indications on the possible algorithms to follow for requesting autoantibody tests in cases of suspected ARD, the majority of clinicians do not follow the guidelines [12–14].

Another aspect to consider is that, in a great many cases, general practitioners use autoantibody tests more to exclude a possible diagnosis of ARD rather than to confirm such, and they ask for tests based on the presence of weak or generic clinical symptoms. This is a real problem for the efficacy of the results that the laboratory can provide to the clinician, since the positive predictive value of a test depends on the pre-test probability that the given patient in fact have the disease for which the test is being performed [15].

In this regard, there are two approaches by laboratories to these problem: on one hand, there are laboratories that offer an "open door" testing service, that is, unrestricted testing of all samples arriving in the laboratory without regard to clinical background [16]; on the other hand, there are pathologists who operate in terms of appropriateness, selecting the best algorithm (adding or deleting tests) according to the results of the screening tests and the suspected diagnosis. In this latter case, it is possible for the clinical pathologist to provide the clinician with an adequate interpretation of the results [17].

There is, for example, consolidated evidence that, in the presence of a negative ANA screening test and in the absence of a consistently suspected diagnosis, it is un-useful to proceed with performing other tests such as those for dsDNA, anti-chromatin, anti-extractable nuclear antigens

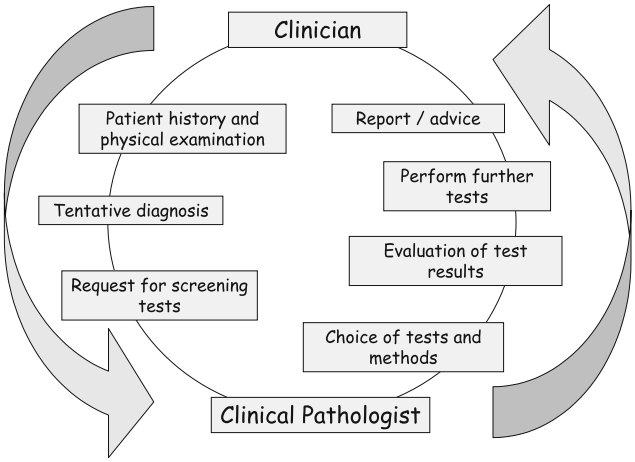

Fig. 1 Optimal diagnostic loop for the serological diagnosis of autoimmune rheumatic diseases

(ENA) or other nuclear and cytoplasmic specific antibodies [17–20]. Furthermore, proteinase 3-ANCA and myeloperoxidase-ANCA should not be ordered if the ANCA IF screening has been found negative [21]. But, the clinician who requests the tests cannot know a priori what the result of the ANA or ANCA test will be, and the request of the follow-up test, always done a priori, may be useless or poorly directed.

In the setting of collaboration with rheumatologists and general practitioners, the most rational strategy may be to set up very simple rules for ordering one or two screening tests based on a tentative diagnosis, encouraging further diagnostic work-up to be done by a laboratory expert in the field [19].

The ideal diagnostic sequence (Fig. 1) should, therefore, initiate in the clinic where the clinician, after carefully recording the clinical history and after making an accurate physical examination of the patient, should formulate a tentative diagnosis and request a first-level test (for example, ANA or ANCA), indicating the suspected diagnosis (for example, symptoms related to myositis; presence of sicca syndrome; presence of Raynaud's phenomenon) or specifying that the request is being made for other motives (such as "to exclude ARD"), increasing, respectively, the positive or negative predictive values of the test results.

In the laboratory, on the basis of first-level tests (for ANA: positivity, end-point titer and fluorescence pattern; for ANCA: presence of a C-ANCA or P-ANCA fluorescence pattern) the clinical pathologist decides whether to perform second-level tests choosing the most appropriate tests and methods (for example, anti-ENA and anti-dsDNA in the case of a positive ANA test; quantitative measuring of PR3 and MPO in the case of a positive ANCA test; in the presence of a cytoplasmatic fluorescence pattern, one uses an immunoblot method to identify direct antibodies against cytoplasmic antigens not present in standard anti-ENA tests; in the same way, in the presence of a centromeric pattern, it is useless to perform an ENA test. Rather, it is more economical and effective to confirm the antibody specificity with a specific test for CENP-B).

The usefulness of the clinical pathologist's intervention will be more evident with borderline or equivocal results. In these cases, the pathologist might decide whether to use other analytic methods and which methods (immunoenzymatic, dot-blot, line-immunoassay, or Western-blot) would be best suited, according to the antibody suspected, to verify and confirm the result.

Once the laboratory procedure has been completed, the report is submitted with interpretive comments to explain to the clinician the significance of the lab data and their implications in terms of diagnostic and prognostic predictivity as well as to offer follow-up steps [22]. This process has already been demonstrated to be effective in other sectors of laboratory diagnostics [23–25].

For these reasons, the effort within clinical laboratories should be to develop laboratory specialists in ARD diagnosis who will have sufficient clinical competence that they will be able to undertake the function of advisor to the physician.

As correctly pointed out by some authors [26], "The crucial question is whether clinical pathologists are to control and improve only the analytical part of testing, including at most pre-analytical aspects, or whether they should share with clinicians the responsibility for appropriate requesting, interpretation, and utilization of laboratory data". In future, we believe that with the constant development of more complex diagnostic tests, such as genomic and proteomic-based assays, clinical interpretations and decisions will become increasingly dependent on laboratory medicine and that the responsibility for keeping clinicians up to date with new developments and optimal use of laboratory results must be in the hands of clinically oriented laboratory experts [20]. In this scenario, laboratory tests and data would then be translated into clinical information that can be used effectively by the physicians.

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