Navigating Lab Tests in Rheumatologic Work-up of Patients

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Physicians are faced with an evolving array of serologic blood tests in Rheumatology. The goal of this article is to assist the physician in the ordering and interpretation of laboratory tests, as they apply to rheumatology. This discussion will be limited to blood tests and will not address radiographic imaging studies.

How do lab tests help us in Rheumatology?

Lab tests can sometimes assist with arriving at a disease-specific diagnosis. This particularly applies to sensitive and specific tests with good positive predictive values for disease.

Sometimes a lab result will help place the patient in a clinical subset of their disease. Thus, lab tests can be instructive in predicting the potential course of a disease and/or the potential end organ of involvement.

Lab tests can also help us monitor the response of disease to medications. For example, in polymyalgia rheumatica or in temporal arteritis, the erythrocyte sedimentation rate (ESR), in conjunction with clinical symptoms, help evaluate the activity of the disease. This guides adjustment of prednisone dosage in these conditions.

Lab tests can also help us delineate drug side effects as we treat a disease process. For example, the liver transaminases (AST and ALT) are important to follow in rheumatoid arthritis (RA) patients treated with methotrexate or leflunomide, to monitor for hepatic toxicity.

Some General Principles:

The Almighty History

Firstly, there are some general principles to keep in mind before turning to the lab for assistance in reaching a Rheumatologic diagnosis. The history or interview of the patient is the most important tool in arriving at a diagnosis. In medicine, the history confers 90% of the diagnosis. Asking the right questions and spending time on the history will bring its rewards.

For example, in dealing with articular complaints, it is very fruitful to pose the question: "Do you have a worst time of day?" Time and time again, patients with inflammatory arthritis will say that mornings are their worst time of day, with pain and morning stiffness.

Another example is the importance of a Rheumatology Functional Enquiry when dealing with a case of possible lupus. Before ordering an anti-nuclear antibody (ANA), it is critical to ask about skin rashes, such as photosensitivity rash or malar rash, oral mucosal ulcers, hair loss, Raynaud's syndrome, sicca symptoms, or inflammatory arthritis features.

The bottom line is that it is important to be a clinician and do a thorough history and physical exam, rather than immediately jumping to immunology lab tests.

Predictive Value of Lab Tests

Before ordering immunologic lab work such as a rheumatoid factor or ANA, it is critical to do one's utmost in arriving at a pre-test probability of a given disease. One wants to critically consider what a lab test will confer as far as post-test probability of a given disease. This is important in deciding when to order a blood test.

Some tests, such as the ANA, are overly sensitive in that the control population lacking the disease will often have a positive test. Some tests are also non-specific, such as the ANA, whereby there are a lot of false positives. Thus, the ANA has a poor positive value for disease such as lupus. The positive predictive value for a test is as follows: true positives over the denomonator of true positives plus false positives. (PPV=TP/TP+FP). Therefore, only order an ANA if you have a reasonable pre-test probablity of disease. The physician must be discriminating when ordering these tests.

The Hematology Profile

Remember to do the basic lab tests first before going to more exotic

Table 1:
Hematology Lab Tests in Rheumatology

Test	Change in Test	Clinical Scenario
Hb	Decreased	Normochromic, normocytic anemia of chronic disease in inflammatory diseases such as RA
Hbt	Decreased	Hypochromic, microcytic anemia of iron deficeincy from GI blood loss in patients on NSAIDs
Hb	Decreased	Coomb's positive hemolotic anemia of SLE
WBC	Decreased	SLE (lymphocytopenia)
WBC	Decreased	Marrow suppression from immunosuppressant drugs
WBC	Increased	Reactive Leukocytosis in Polyarteritis Nodosa, Chrug Strauss vasculitis (eosinophilia), Adult Onset Stills Disease (with marked increased ferritin)
WBC	Increased	Steroid leukocytosis (with demargination of polyps)
Platelets	Decreased	Idiopathic thrombocytopenic purpura (ITP) picture of SLE
Platelets	Decreased	Gold-induced thrombocytopenia in RA
Platelets	Increased	Reactive thrombocytosis inflammatory disease such as RA

serologic testing. The complete blood count (CBC) is important to test and follow in inflammatory rheumatic disease (Table 1).

The ESR and /or CRP

ESR is an overly sensitive and non-specific test in medicine, but can be informative in Rheumatology practice. The ESR is often high in active RA. Some patients are concordant for the ESR and their disease activity, such that the ESR goes up with active disease and lowers with control of the disease. The ESR is of great importance in the diagnosis and follow-up of polymyalgia rheumatic (PMR) and temporal arteritis. Some cases of PMR can run a normal ESR even at the time of onset; this makes diagnosis and monitoring of disease activity and corticosteroid treatment challenging.

The C-reactive protein (CRP) is another acute phase reactant that can be high in inflammation or infection. Like the ESR, the CRP is very sensitive and very non-specific.

Biochemistry Lab Tests

The creatine kinase (CK) can be very high in inflammatory muscle disease such as polymyositis (PM) or dermatomyositis (DM), which present with proximal muscle weakness. A less than two-fold elevation of CK is probably insignificant.

Liver enzymes should be done as a baseline and followed-up every two months, particularly the transaminases (AST and ALT), with use of methotrexate or leflunomide.

The creatinine and urinalysis are very useful tests and are critical to follow at least every six to eight months in any patient with lupus or vasculitis, no matter how mild. This is an important principle, as we do not want to lose track of possible evolution to renal involvement and progression.

Rheumatoid factor (RA factor) and Cyclic Citrullinated Peptide (CCP)

In established RA, by one to two years of disease, 85% of patients are RA factor positive. RA factor can occur with normal aging. Many patients have a borderline RA factor which is of questionable significance. The ordering physician must correlate the lab test with the clinical presentation of the patient. Only test for RA factor in the setting of inflammatory joint pain.

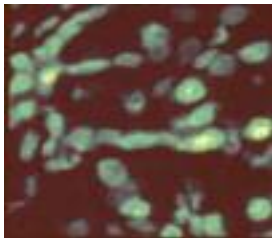
If the RA factor is negative or equivocal in the setting of inflammatory joint complaints, the specialist may elect to order a CCP. This is a test for RA with fair sensitivity and great specificity. Still, a significant percentage of patients with RA remain seronegative (RA factor and CCP negative) throughout their disease course. In many jurisdictions only the rheumatologist can order the CCP.

Anti-nuclear Antibodies (ANA)

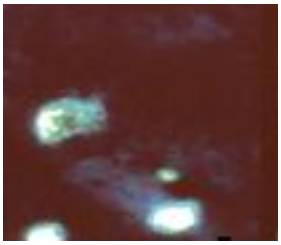
As discussed earlier under "the almighty history," order an ANA if and only if the Rheumatology Functional Enquiry makes you suspect systemic lupus erythematosus (SLE) or some other collagen vascular disease (CVD). Such other CVDs would include Sjogren's syndrome, mixed connective tissue disease (MCTD), scleroderma or polymyositis (PM).

The ANA is an immunoflurorescence slide test and is reported as a titre or dilution. The higher the titre, the more clinically significant it may be. However, the ANA is not a good

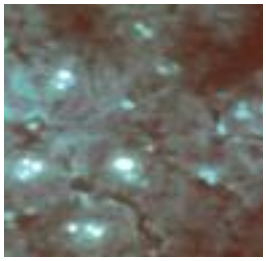
Figure 1: ANA Patterns



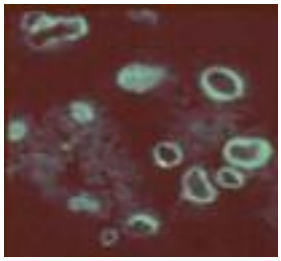
• Homogeneous Pattern (most common pattern in SLE and in controls)



• Speckled Pattern (2nd most common pattern in SLE, typical pattern for scleroderma and Sjogren's syndrome)



• Nucleolar pattern (makes one wonder about scleroderma)



• Peripheral or rim pattern (specific for SLE but not seen often)

positive predictive value test for SLE or other CVDs. It is an overly sensitive and non-specific test, often present in the control population of women. Newer assay techniques for ANA are being developed. The main patterns of immunofluorence for ANA testing are shown in Figure 1; other patterns can occur, but are beyond the scope of this paper.

A negative ANA really detracts from a diagnosis of SLE. In an ill patient with multi-organ disease, a negative ANA almost rules out SLE.

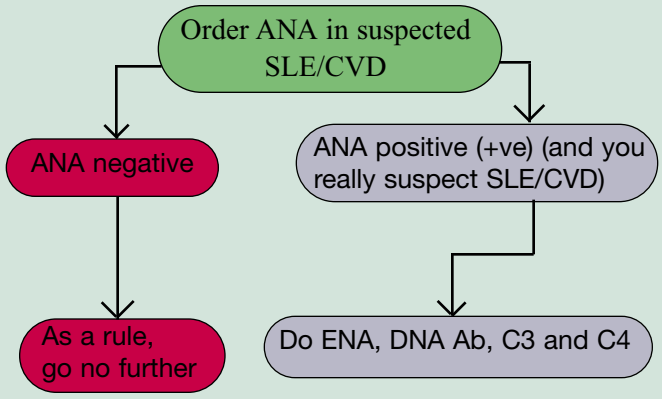
Another pattern of ANA testing, the anti-centromere pattern, is characteristic of the CREST variant of scleroderma.

If the ANA is positive and you really suspect SLE or some other CVD then also go on to an extractable nuclear antigen (ENA). In suspected SLE, when the ANA is positive go on and do an anti-DNA antibody (Ab) and a C3 and C4 (Figure 2).

Extractable Nuclear Antigens (ENAs)

These are done after a meaningfully positive ANA, and can further guide diagnosis and denote subsets of disease. There are six main patterns as follows:

Figure 2: Ordering of ANA, ENA and DNA Ab and C3, C4



* CVD = Collagen Vascular Disease

Do not order ANA, DNA Ab and C3/C4 all at once the first time. Order ANA first and then based on result and clnical impression, one can go further

Do not keep following ANA and ENA; do only once as these do not fluctuate with disease activity. Do follow DNA Ab and C4 in concordant patient with lupus

1. Smith (Sm): diagnostic for SLE but not often seen
2. Ribonucleoprotein (RNP): can be positive in SLE or in MCTD
3. SSA (Ro)
4. SSB (LA): these (#3 and #4) can be positive in SLE or in Sjogren's syndrome. They can portend risk of neonatal lupus or congenital heart block (rare)
5. Topisomerase/ SCL-70 portends a risk of diffuse cutaneous scleroderma/systemic sclerosis
6. Jo-1: risk of interstitial lung disease in polymyostis/ dermatomyositis

An increasing list of ENAs have been developed, but are beyond the scope of this article

Anti–DNA Antibody (Ab)

This is an antibody to native, double stranded DNA. In moderate to high titre it is specific and diagnostic for SLE. In a low titre, it may be non-specific.

The anti-DNA Ab is positive in about 40 to 50% of SLE patients. It can fluctuate with disease activity in a concordant patient, increasing in cases of active disease. Concordance denotes that the lab test mirrors the clinical activity of disease. See Figure 2 for when to order an anti-DNA Ab.

Complements—C3 and C4

These proteins are consumed by immune complexes and may be low in active SLE, or in some cases, vasculitis. They will normalize with inactive or adequately treated disease in concordant cases.

Cryogobulins

Only order these if you suspect mixed cryoglobulinemia, a form of small vessel vasculitis often presenting with palpable purpura. Patients with mixed cryoglobulinemia are almost always Hepatitis C positive as well. The cryoglobulines are reported as a "cryocrit" and it is important that the blood sample be handled properly by the lab. Most patients with mixed cryoglobulinemia have a significant rheumatoid factor, but do not have RA.

Anti-Neutrophil Cytoplasmic Antibody (ANCA)

ANCA is significant to ANCA Associated Vasculitis (AVA). There are two main patterns: cytoplasmic ANCA (C-ANCA) and peri-nuclear ANCA (P-ANCA). C-ANCA has a high concordance with Wegener's Granulomatosis, a form of vasculitis. It can also be positive in idiopathic pauci-immune glomerulonephritis (GN) and occasionally in Churg Strauss vasculitis. C-ANCA is an antibody to proteinase-3. Overall, it confers a high predictive value of Wegener's in the appropriate clinical setting. This test is such a valuable diagnostic tool that it often supplants the need for tissue biopsy in Wegener's, as it is quite disease-specific.

The P-ANCA pattern is positive in many diseases, and even non-disease states. The lab automatically goes ahead and does an enzyme linked immunosorbent assay (ELISA) on P-ANCA positive sera for myeloperoxidase (MPO). MPO is disease-specific.

P-ANCA that is MPO positive is highly supportive of microscopic polyangiitis (MPA); results can be positive in idiopathic pauci-immune GN.

Use ANCA in work up of vasculitis and in the setting of pulmonary/renal syndromes, *etc.*

Antiphospholipid Antibody (APA) Testing

There are a number of lab tests for antiphospholipid syndrome (APS). This syndrome is characterized by excessive clotting risk, or risk of fetal loss due to placental insufficiency. Testing should be done as part of a hyper-coagulation work up and in recurrent fetal loss. Every woman with lupus should have this panel of tests ordered before conception. If it is positive, a Rheumatologist and/or Hematologist should be consulted. The three tests ordered are as follows:

1. PTT, writing on the requisition, "rule out lupus anticoagulant (LAC)." If lupus is suspected from PTT results, the lab may elect to do further testing; including mixing studies, a kaolin clot test and a diluted Russell viper venom test (DRVVT)
2. Anti cardiolipin antibody (ACA) is done against IgG and IgM and is part of the set of antiphospholipid tests
3. Finally Beta 2-glycoprotein (BGP) is done as a part of antiphospholipid testing

These tests should be repeated at about 10 weeks, since their detection can fluctuate. In positive patients, at least low dose ASA is usually indicated and s.c. heparin may be indicated during pregnancy for some women. Some patients with major clotting problems who are not pregnant may need warfarin.

HLA-B27

This is an expensive test and lacks optimal positive predictive value for seronegative spondyloarthropathies such as ankylosing spondylitis (AS).

Thus, we should avoid ordering it. Instead, take a history for inflammatory back pain, including the following features—insidious onset under age 40, back pain that gets better with exercise and worsens with inactivity, morning stiffness over ½ hour of duration, and night pain. This clinical approach is the best way of detecting AS. Imaging tests of the sacroiliac joints may then be undertaken after physical exam.

Concluding Remarks

There is a plethora of serologic Rheumatology lab tests, many of which have evolved in the past decade. Some of these serological tests represent great steps of medical progress. However, we should not order them indiscriminantly. Always be a clinician first. Take a thorough history and Rheumatology Functional Enquiry and examine the patient thoroughly first. These lab tests can aid in diagnosis and in some cases, the outlook for a patient's disease. Still, do not treat the lab tests as a rule; treat the patient. If we use these lab tests appropriately, they will serve to enhance patient care.

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