Systemic lupus erythematosus: diagnosis for the non-specialist

This review discusses the pitfalls in placing too much reliance on an antinuclear antibody test result for the diagnosis of systemic lupus erythematosus, outlines a practical approach to patients in whom this illness is suspected, and gives guidance on how to request these tests sensibly.

GPs and non-rheumatologists often indiscriminately request the antinuclear antibody (ANA) test for patients presenting with joint pains. Patients with a positive ANA result, irrespective of their wider clinical picture, are then referred to the rheumatologist 'to exclude systemic lupus erythematosus (SLE)'. Most patients referred for this reason have no evidence of SLE or other connective tissue disease (Lee et al, 2003). This not only wastes resources but also leads to unnecessary anxiety for the patient. Although immunological test results form the basis of a diagnosis of SLE in patients with typical clinical involvement of multiple systems, the clinician needs to be aware of the limitations of these tests.

Table 1. Some causes of a positive antinuclear antibody result

Autoimmune rheumatic diseases	Systemic lupus erythematosus (present in > 95% of patients)
	Mixed connective tissue disease (> 95%)
	Systemic sclerosis (about 75%)
	Sjögren's syndrome (about 75%)
	Polymyositis (about 25%)
	Rheumatoid arthritis (about 25%)
Non-rheumatic autoimmune diseases	e.g. Grave's disease, type 1 diabetes, idiopathic thrombocytopenic purpura, myasthenia gravis, autoimmune liver disease
Infection	Any infection (especially hepatitis B and C, human immunodeficiency virus, infectious mononucleosis, Gram-negative bacterial infections, malaria)
Neoplasia	Leukaemias
	Lymphomas
	Solid tumours
	Melanoma
Miscellaneous	Idiopathic pulmonary fibrosis
	Inflammatory bowel disease
	Primary biliary cirrhosis
Drugs	Procainamide, hydralazine, minocycline, isoniazid, sulphasalazine
Health	Especially elderly and pregnant women, relatives of patients with autoimmune diseases

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What are the pitfalls of the ANA test for diagnosis of SLE?

ANA refers to a family of autoantibodies that are directed against constituents of cell nuclei such as single or double-stranded DNA (dsDNA), histones, centromere, enzymes such as topoisomerase and various proteins complexed with RNA. Protein antigens complexed with RNA (collectively known as ENA or extractable nuclear antigens) include Ro, La, Sm and RNP, and are either named after the patient in whom they were first detected (Robert or Ro, Lavaine or La, Smith or Sm) or the antigen that is targeted (ribonucleoprotein or RNP).

ANA is encountered in a range of conditions

ANA is encountered in a variety of conditions apart from SLE (Illei and Klippel, 1999) (*Table 1*). First, it is not uncommon for a perfectly healthy immune system to produce some ANA against self-antigens from time to time. One study in healthy individuals noted a prevalence of 32% for an ANA titre of 1/40, 15% for a titre of 1/80, 5% for a titre of 1/160 and 3% for a titre of 1/320 (Tan et al, 1997). Low titre ANA, especially in elderly women, should be viewed with caution.

Second, ANA could be produced if infection occurs with an organism whose epitope is similar to self-antigens ('molecular mimicry') or when antigenicity of self-antigens is altered, for example, by infection, cancer or drugs.

Lastly, loss of 'immunological tolerance' (ability to distinguish between self and foreign antigens) results in production of various autoantibodies, including ANA. Thus, ANA are associated with several other autoimmune rheumatic as well as non-rheumatic conditions.

The presence of ANA is, therefore, neither specific nor sufficient on its own for diagnosis of SLE.

Laboratory methods for ANA testing are not very specific for a diagnosis of SLE

An ideal laboratory test would detect ANA in all patients with SLE and in none of those with other conditions, but such a method does not exist.

A major advantage of currently used laboratory methods for detection of ANA is that they are extremely sensitive for a diagnosis of SLE – more than 99% of patients with SLE have a positive result. This means that a negative ANA result virtually excludes SLE as a diagnosis. However,

the specificity for a diagnosis of SLE is only 60% (Kavanaugh et al, 2000; Solomon et al, 2002). Thus, most other conditions that are associated with ANA also give a positive result with currently used methods.

When an ANA test is requested indiscriminately, the positive predictive value for diagnosis of SLE or any other rheumatic disease is only around 11% (Slater et al, 1996). The temptation to indiscriminately request ANA in all patients with joint pains or to label them as 'SLE' solely on the basis of a positive ANA test should be resisted.

In which patients should an ANA test be requested?

SLE is associated with numerous immune abnormalities that could result in a variety of manifestations in multiple organ systems (*Table 2*). Hence, the first requirement for diagnosing SLE is to look for clinical and/or laboratory evidence of multisystem disease. The positive predictive value of an ANA test is improved when more systems are involved clinically (Liang et al, 1980). American College of Rheumatology (1999) guidelines suggest that an ANA test should only be requested when patients have clinical and/or laboratory manifestations affecting two or more organ systems, i.e. if the pretest probability of SLE (or another connective tissue disease) appears high.

In patients presenting with joint pains (the commonest reason for ANA test request), it is useful to look for extra-articular manifestations as described in *Tables 2* and *3*.

Constitutional

Constitutional symptoms such as fever (in the absence of infection), tiredness, weight loss and arthralgia are common. Non-specific arthralgia and fatigue are among the commonest manifestations of SLE, being present in a vast majority of patients at presentation. While an ANA test request is not unreasonable as a 'screening test' in patients presenting with joint pains and tiredness, positive test results should not lead to a diagnosis of SLE in the absence of other manifestations (see later).

Mucocutaneous

Photosensitive skin rashes are common. Some patients do not develop frank rashes but a flare of systemic symptoms such as arthralgia and fatigue, or even simply discomfort or burning in the skin following exposure to sunlight, which is also a helpful pointer.

The erythematous 'malar rash', described as the most characteristic manifestation of lupus, occurs in less than a third of patients.

A history of recurrent oral or nasal ulcers is also useful, although this is very non-specific.

Haematological

The commonest manifestation is perhaps anaemia of chronic disease but this is non-specific. The presence of haemolytic anaemia, leucopenia, lymphopenia or thrombocytopenia provide more valuable clues.

For reasons that are not entirely clear, SLE is more common among certain races, e.g. African Americans and Chinese. Women of reproductive age are predominantly affected, because oestrogens stimulate the immune system, while androgens are protective (Mok and Lau, 2003). An increased index of suspicion for SLE is required in young and middle-aged African American or Chinese women with suggestive symptoms but the diagnosis should not be overlooked outside these groups (Maddison, 2002).

Neuropsychiatric

SLE should be included in the differential diagnosis for unexplained neuropsychiatric manifestations (in the absence of other causes such as infective, metabolic or

Table 2. Systemic lupus erythematosus manifestations explained by pathogenesis

Pathogenesis	Examples of manifestations
Production of cytokines	Fever (in the absence of infection), tiredness, arthralgia, weight loss and anaemia of chronic disease
Immune complex deposition (commonly in synovium, skin, kidneys, serosal surfaces, lungs, and blood vessels)	Inflammatory arthritis, photosensitive skin rashes, glomerulonephritis, pleurisy, pericarditis, interstitial lung disease, mouth ulcers, vasculitis
Direct antibody-mediated attack	Haemolytic anemia (red cell antibodies), thrombocytopenia (anti-platelet antibodies), leucopenia and lymphopenia (lymphocytotoxic antibodies), and neuropsychiatric manifestations such as depression and psychosis (anti-ribosomal-P antibodies)
Associated syndromes	Recurrent arterial or venous thrombosis, recurrent miscarriages (anti-phospholipid antibody syndrome), dry eyes and mouth (Sjögren's syndrome)

Table 3. Useful clues from laboratory tests and imaging

'Routine' laboratory tests	Leucopenia, lymphopenia or neutropenia
	Thrombocytopenia*
	Haemolytic anaemia
	Elevated erythrocyte sedimentation rate and normal C-reactive protein* (C-reactive protein is often normal, unless there is coexistent infection, because of suppression of Th1 cytokine production)
	Abnormal urinalysis with presence of red cell casts, proteinuria or sterile pyuria (implying possible glomerulonephritis)
Immunological tests	Positive antinuclear antibody
	Positive double-stranded DNA antibodies (highly specific)
	Positive anti-Smith antibodies (highly specific)
	Low complement levels (C3 and C4)* (commonly caused by consumption by immune complexes)
	Presence of anti-phospholipid antibody (anti-cardiolipin antibody or lupus anticoagulant)
Radiological findings	Absence of erosive changes*

* Presence of thrombocytosis, very high C-reactive protein in the absence of infection or serositis, elevated complement levels or presence of erosive changes on X-rays tend to rule out a diagnosis of systemic lupus

toxic) especially when they occur in young women. Nineteen different neuropsychiatric syndromes have been described in SLE, with cognitive dysfunction, headache, mood disorder, cerebrovascular disease, seizures, depression and psychosis more common.

Pulmonary

Pleurisy is common. Other pulmonary manifestations are rare at the time of presentation.

Cardiac

Pericarditis is the most common cardiac manifestation although this is often asymptomatic.

Renal

Abnormal urinalysis with presence of red cell casts, proteinuria or sterile pyuria may indicate renal involvement with glomerulonephritis.

Which antibody tests are helpful or unhelpful in a patient with a positive ANA test?

Testing for antibodies against individual nuclear antigens is more disease specific. For example, ANA in patients with SLE are targeted against single and dsDNA, histones, Sm, Ro, La and RNP. Among these, presence of anti-dsDNA or anti-Sm is highly specific (close to 100%) for SLE, as they are seldom seen in patients without SLE (Kavanaugh and Solomon, 2002). Anti-dsDNA also correlates with activity of disease and renal involvement in patients with SLE (ter Borg et al, 1990).

However, anti-dsDNA is present in only about 60% of patients with SLE. Anti-Sm is not very sensitive either, being present in only about 30% of patients (predominantly in African Americans) (Kavanaugh et al, 2000). Thus, although the presence of either of these antibodies strongly indicates a diagnosis of of SLE, their absence does not exclude the diagnosis. Positive DNA antibodies could be reported (depending on the method used) from the presence of low titres of IgM anti-dsDNA or single-stranded DNA antibodies, both of which are found in healthy patients. The higher specificity of DNA antibodies for diagnosis of SLE only applies to high titre immunoglobulin G antibodies to dsDNA (Hahn, 1998).

Antibodies other than anti-dsDNA and anti-Sm are less specific for SLE because they are also found in patients with other connective tissue diseases.

Table 4. American College of Rheumatology classification criteria for systemic lupus erythematosus

Malar rash
Discoid rash
Photosensitivity
Oral or nasopharyngeal ulcers
Non-erosive arthritis
Pleurisy or pericarditis
Renal disorder (proteinuria (> 0.5 g/day or > 3+) or casts)
Neurological disorder (seizures or psychosis – in the absence of known causes)
Haematological disorder (haemolytic anaemia with reticulocytosis or leucopenia < 4000/mm^3 on two or more occasions or lymphopenia < 1500/mm^3 on two or more occasions or thrombocytopenia < 100 000/mm^3 in the absence of offending drugs)
Positive antinuclear antibody
Immunological disorder (anti-DNA or anti-Smith or antiphospholipid antibodies)

Presence of four of these eleven criteria is required to make a diagnosis of systemic lupus erythematosus. From Tan et al

Which patients are likely to present diagnostic difficulties?

Diagnosis is easy when more systems are involved because the differential diagnosis becomes more narrow. Presence of 'hard' features such as nephritis, haemolytic anaemia, thrombocytopenia or characteristic lupus rash is particularly helpful. Thus a positive ANA test is more likely to be the result of SLE in a patient presenting with inflammatory joint pain, photosensitive skin rashes, thrombocytopenia and nephritis than in someone presenting with only one or two non-specific manifestations, e.g. arthralgia or fatigue (Kavanaugh et al, 2000). As discussed above, the presence of specific antibodies such as anti-dsDNA and anti-Sm is also very helpful, especially in the presence of fewer or non-specific manifestations.

The real problem arises in patients with only non-specific symptoms, a positive ANA test and negative DNA and Sm antibodies. Because there is no 'cut-off' ANA titre that reliably distinguishes patients with SLE or other autoimmune diseases from those with other conditions (Egner, 2000), and because the differential diagnosis of individual non-specific manifestations is broad, alternative causes for similar clinical presentation as well for a positive ANA test should be considered in such situations.

For example, both SLE and fibromyalgia could present with joint pains, tiredness, chest wall pain, cold hands, cognitive dysfunction, depression, migraine headaches and a positive ANA test (Bennett, 1997; Blumenthal, 2002). Another example is patients who are referred with facial rash and a positive ANA test. The differential diagnosis of facial rash is broad, and includes acne rosacea, contact dermatitis and seborrhoeic dermatitis. One study found that in most patients referred to the 'lupus clinic' with skin rash and a positive ANA test, the skin rash was caused by acne rosacea (Black et al, 1992).

Are classification criteria useful for clinicians?

The American College of Rheumatology has devised criteria for classification of patients with SLE (*Table 4*) (Tan et al, 1982; Hochberg, 1997). Although classification criteria, in general, are devised for epidemiological and research purposes rather than for clinical diagnosis, they can be helpful for evaluating individual patients. SLE is diagnosed when four out of the eleven criteria listed in *Table 4* are present. These criteria have a specificity of 95% but the sensitivity is only around 85%,

which means that some patients with SLE, especially those with early disease, do not fulfil these criteria (Perez-Gutthann et al, 1991). In some patients, especially those who fulfil fewer than four criteria, the diagnosis might become apparent with time, as new symptoms arise.

Which patients with positive ANA tests should be referred?

If the ANA test was not requested indiscriminately in the first place, then ideally all patients with a positive ANA test should be referred unless the results are positive in a low titre (1/40), and there is an alternative explanation, e.g. thyroid disease (*Figure 1*). Patients with connective tissue diseases seldom have positive ANA in a low titre (<1/80).

Even if the ANA result is strongly positive, the non-specialist should not discuss the results with the patient, as this can cause anxiety that is difficult to remove even if the result is a false positive. Also, as both SLE and psychosomatic illness share the same constellation of symptoms, undue emphasis on an abnormal result before referral may be particularly unhelpful in such patients.

Conclusions

The first requirement for diagnosis of SLE is to look for clinical involvement of multiple organ systems. However, most patients present with vague, non-specific symptoms. ANA should be requested only if the pre-test probability of SLE or other connective tissue disease seems high. Although a negative ANA result makes it extremely unlikely that SLE is the cause of the illness in question, a positive ANA result on its own is not sufficient to diagnose SLE. Immunological test results should always be interpreted in the context of the whole clinical picture. Anti-dsDNA and anti-Sm are both highly specific (close to 100%) for diagnosis of SLE, but neither is very sensitive. **BJHM**

Conflict of interest: none.

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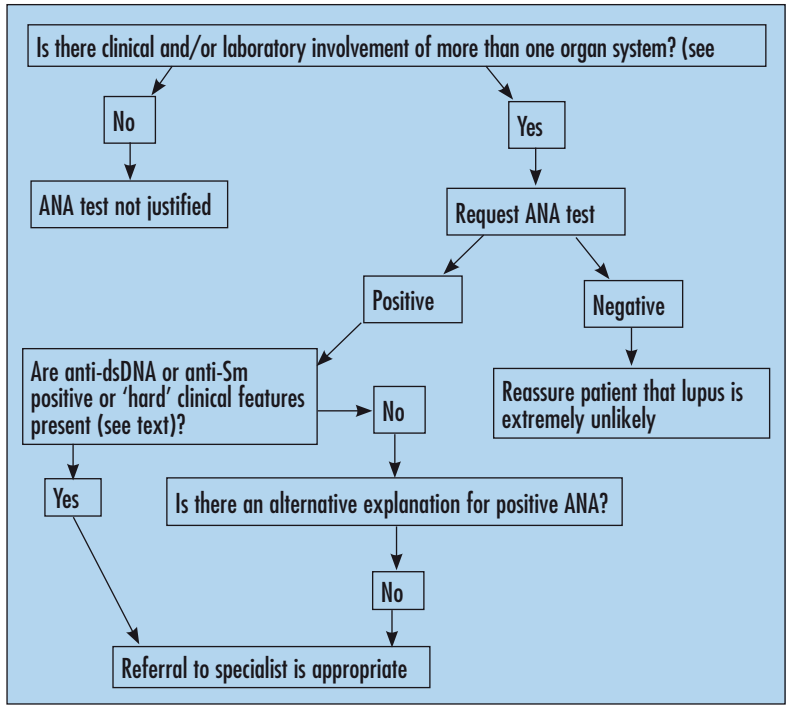
Figure 1. Flow chart to guide antinuclear antibody (ANA) test request and referral to specialist.



KEY POINTS

- The first requirement for diagnosis of systemic lupus erythematosus (SLE) is to look for clinical involvement of multiple organ systems. However, most patients present with vague and non-specific symptoms, posing a diagnostic challenge.
- Antinuclear antibody (ANA) should be requested only if the pre-test probability of SLE or other connective tissue disease appears high.
- Although a negative ANA result makes a diagnosis of SLE extremely unlikely, a positive ANA result is insufficient on its own for a diagnosis, so immunological test results should be interpreted in the context of the whole clinical picture.