



Investigating the patient with a positive antinuclear antibody

Each month we present authoritative advice on the investigation of a common clinical problem, specially written for family doctors by the Board of Continuing Medical Education of the Royal Australasian College of Physicians.

IAN GOTIS-GRAHAM

MB BS (Hons), FRACP, PhD

Dr Gotis-Graham is a Visiting Rheumatologist, Liverpool Hospital, Liverpool, NSW.

Series Editor

CHRISTOPHER S. POKORNY

MB BS, FRACP

Dr Pokorny is Honorary Secretary, Board of Continuing Education, Royal Australasian College of Physicians, and a gastroenterologist in private practice, Sydney, NSW.

The test for antinuclear antibody (ANA) is often performed in patients who have musculoskeletal symptoms or symptoms that are suggestive of an autoimmune disease.

A positive ANA result is not limited to systemic autoimmune diseases such as systemic lupus erythematosus and scleroderma. It can be seen in organ specific autoimmune diseases involving the thyroid, lung and liver.¹ It also occurs in a variety of conditions that are not autoimmune, such as chronic infections, malignancy and haematological disorders (Table 1). A positive ANA can be found in healthy individuals and does not necessarily indicate disease.

Approach to the patient with a positive ANA

The correct interpretation of a positive ANA depends on a thorough history and physical examination, careful consideration of the clinical situation, and appropriate laboratory investigations.

When assessing a patient with a positive result, an important initial step is to exclude systemic and organ specific autoimmune diseases.

Is it systemic autoimmune disease?

When a systemic autoimmune disease is present, the patient will usually have suggestive clinical features, such as:²

- peripheral symmetrical polyarthritis (pain and swelling in the small joints of the hands and feet)
- Raynaud's phenomenon
- skin rashes (Figure 1)
- sclerodactyly
- sicca symptoms
- proximal muscle weakness.

A positive ANA is essential to the diagnosis of some autoimmune diseases such as systemic lupus erythematosus.

When the ANA is positive and the clinical features are suggestive of a systemic autoimmune disease, testing for disease associated autoantibodies (Table 2) will help you to differentiate between these conditions.

Difficulties arise when the clinical manifestations develop over a long period. A positive ANA may be due to early, undifferentiated systemic autoimmune disease. A patient may present with

IN SUMMARY

- The ANA test is a sensitive test, important in confirming a clinical impression of autoimmune disease. However, a positive result is not specific for autoimmune disease and may not be relevant to the patient's presenting problems.
- The correct interpretation of a positive ANA depends on a thorough history and physical examination, careful consideration of the clinical situation, and appropriate laboratory investigations.
- The ANA titre and staining pattern are less important in determining the relevance of the test result.
- A positive ANA may be due to early, undifferentiated autoimmune disease.
- A positive ANA can be found in normal healthy individuals. The incidence of a positive ANA increases with age.

a positive ANA and possibly a disease associated autoantibody, but have no definitive clinical features. The patient should be observed over time, and further investigations may be warranted.

A positive ANA result can also be seen in systemic autoimmune diseases that are not defined by ANA. Almost 30% of patients with rheumatoid arthritis have low to moderate levels of ANA. A positive ANA can be seen in patients with vasculitis; however, not all patients with vasculitis have a positive ANA. Vasculitis should be suspected in patients with an appropriate clinical history and physical findings, regardless of the ANA result.

Is it organ specific autoimmune disease?

A positive ANA is sometimes seen in patients with autoimmune disease limited to specific organs such as thyroid, lung or liver.¹ If the history and physical examination are suggestive of these conditions, it may be appropriate to perform further investigations such as thyroid stimulating hormone, thyroid autoantibodies, liver function tests, antimitochondrial antibodies or a chest x-ray.

If not autoimmune disease, what next?

In many patients, the finding of a positive ANA can be unexpected. Systemic and organ specific autoimmune diseases should be excluded as outlined above. The approach should then include:

- a review of medications to exclude drug induced ANA
- a family history to identify ANA genetic diathesis
- a chest x-ray and further respiratory investigations to exclude interstitial lung disease and pulmonary hypertension
- liver function testing and a full blood count to exclude unsuspected hepatic or haematological disease
- testing for chronic infection and malignancy according to the clinical situation.



Figure 1. The butterfly facial rash of systemic lupus erythematosus. Clinical features are important in interpreting a positive ANA.

Drug induced ANA

There is an ever expanding list of medications that can induce a positive ANA. The drugs include procainamide, hydralazine, isoniazid and minocycline. Some new biological therapies, such as interferon for multiple sclerosis and anti-tumour necrosis factor receptor therapy for rheumatoid arthritis, are associated with the development of ANA.

Despite cessation of the offending drug, the ANA may remain positive for many months or years. Most patients with drug induced positive ANA are asymptomatic; however, some patients develop clinical syndromes suggestive of drug induced lupus or drug induced polymyositis.

ANA genetic diathesis

Studies have shown that up to 50% of first degree relatives of patients with systemic lupus erythematosus, Sjögren's syndrome or scleroderma have a positive ANA.³ These relatives remain normal and rarely develop systemic autoimmune diseases.

What if initial investigations are inconclusive?

In some people, the history, physical examination and initial investigations

Table 1. Causes of a positive ANA result

Systemic autoimmune disease

Systemic lupus erythematosus
Scleroderma
Mixed connective tissue disease
Polymyositis and dermatomyositis
Sjögren's syndrome
Rheumatoid arthritis
Vasculitis

Thyroid disease

Hashimoto's thyroiditis
Graves' disease

Lung disease

Cryptogenic fibrosing alveolitis
Primary pulmonary hypertension
Asbestosis

Liver disease

Chronic active hepatitis
Primary biliary cirrhosis
Alcoholic liver disease
Hepatitis B

Drug induced ANA

Malignancy

Lymphoma
Leukaemia
Solid tumours

Haematological disease

Idiopathic thrombocytopenic purpura
Autoimmune haemolytic anaemia

Chronic infection

Subacute bacterial endocarditis
Tuberculosis
Malaria
Parasitic diseases
Leprosy

are not suggestive of any of the above-mentioned conditions. Numerous studies have documented in normal, healthy people a positive ANA at titres of 1:80 or less. The incidence of a positive ANA increases with age, so that 20 to 25% of

continued

people over the age of 60 years have a positive ANA.³

The ANA test should not be performed as a screen for autoimmune disease in patients who have little clinical evidence of such conditions. A positive ANA finding in such a patient can be difficult to interpret and may cause patient anxiety.

When to refer to a rheumatologist

Refer to a rheumatologist if:

- there are clinical symptoms and signs of a systemic autoimmune disease, regardless of the ANA result
- the ANA titre is moderate to high (greater than 1:640)
- the results are positive both for ANA and for a disease associated autoantibody (see Table 2).

Interpretation of titre and staining pattern

Titre

When an ANA test is reported, the titre and staining pattern are given. The test is very sensitive. A low level ANA titre, such as less than 1:80, may not be clinically relevant. A moderate to high result, such as an ANA greater than 1:640, should prompt exclusion of an autoimmune disease. However, a high titre alone is not diagnostic of disease. If the clinical examination and initial investigations are not diagnostic of an autoimmune disease, the patient should be referred and

Table 2. Autoimmune diseases and associated autoantibodies

Diseases	Autoantibodies
Systemic lupus erythematosus	Anti-double stranded DNA; anti-Sm
Drug induced lupus	Antihistone
Sjögren's syndrome	Anti-SSA; anti-SSB
Scleroderma	Anti-Scl 70; anticentromere
Mixed connective tissue disease	Anti-RNP
Polymyositis/dermatomyositis	Anti-Jo1

observed, to exclude development of such a condition.

In patients who have no symptoms or signs of autoimmune disease and low ANA titres, significant disease is unlikely to be present.

The ANA titre is less relevant in patients who have unmistakable clinical evidence of systemic autoimmune disease. For example, patients with systemic lupus erythematosus with active renal or cerebral disease can have a low titre ANA.

Staining pattern

The ANA staining pattern is usually described as rim, peripheral, speckled, nucleolar or centromere (Figures 2a and b). The centromere pattern is associated with the CREST variant of scleroderma. The other patterns are of limited use in diagnosis. Different patterns were thought to be associated with different types of

autoantibodies. However, pattern recognition has largely been replaced by autoantibody testing (Table 2).

Conclusion

A positive ANA result will be expected in patients with symptoms and signs consistent with a systemic autoimmune disease. In this situation, a provisional diagnosis of a systemic autoimmune disease can often be made before the ANA result is available. Most patients with a positive ANA result do not have a clinical picture suggestive of systemic autoimmune disease. In these patients, a thorough history and physical examination are needed to correctly interpret the significance of the ANA. MT

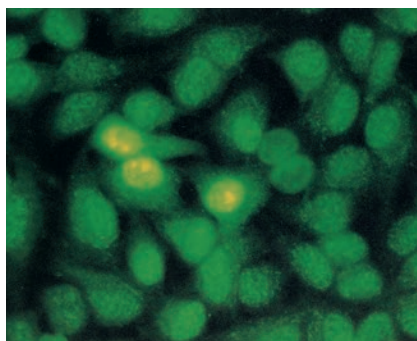
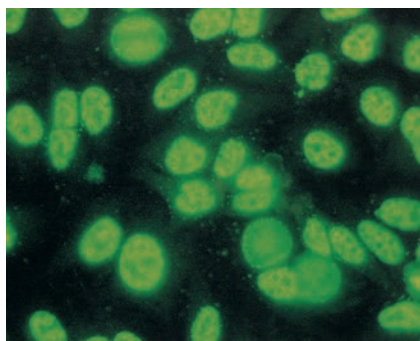
References

1. Kurki P, Gripenberg M, Teppo AM, Salaspuro M. Profiles of antinuclear antibodies in chronic active hepatitis, primary biliary cirrhosis and alcoholic liver disease. *Liver* 1984; 4: 134-138.
2. Hahn BH. Antibodies to DNA. *N Engl J Med* 1998; 338: 1359-1368.
3. Tan EM, Feltkamp TE, Smolen JS, et al. Range of antinuclear antibodies in 'healthy' individuals. *Arthritis Rheum* 1997; 40: 1601-1611.

Acknowledgements

I thank Dr Allan Sturgess, St George Hospital, Sydney, for his helpful comments and for the images in Figure 2.

COURTESY OF DR ALLAN STURGESS, SYDNEY



Figures 2a and b. Immunofluorescence staining patterns for ANA. a (left). Strongly positive ANA in a speckled pattern, typical of a patient with Sjögren's syndrome. b (right). ANA positive in only three nuclei, a pattern typical of SSA antibodies.