ECRONICON OPEN ACCESS

EC CARDIOLOGY
Case Report

Careful Not to be Lead Down the Garden Path

Alvin Ee Zhiun Cheah[1], Purvish Patel[1,2] and Seshasayee Narasimhan[1,3,4,5]*

[1]*Internal Medicine, Manning Base Hospital, Taree, NSW, Australia*

[2]*Nephrology, Manning Base Hospital, Taree, NSW, Australia*

[3]*Cardiology, Manning Base Hospital, Taree, NSW, Australia*

[4]*Conjoint Senior, University of Newcastle, Callaghan, NSW, Australia*

[5]*Adjunct Senior Lecturer, University of New England, Armidale, NSW, Australia*

***Corresponding Author:** Seshasayee Narasimhan, Cardiology, Manning Base Hospital, Taree, NSW, Australia.

Received: February 02, 2019; **Published:** February 28, 2019

Abstract

Antinuclear antibodies (ANA) are autoantibodies produced against nuclear antigens which is an indispensable tool that improves diagnostic efficiency of systemic rheumatological conditions and possible identification of neoplasia in certain patient populations with unexplained diagnosis. The staining pattern may be beneficial in assisting the clinician to obtain an appropriate diagnosis. However, ANA can also be significantly elevated in non-rheumatological conditions such as malignancy and healthy individuals. Due to its high false positive results clinicians should be aware of its limitations and interpret the results based on clinical judgement. This article depicts a case of cardiac tamponade with persistently significant elevated ANA tires where the cause was later found to be secondary to malignancy.

Keywords: *Pericardial Effusion; Antinuclear Antibodies (ANA); Heart Failure*

Learning Objective

The role of ANA in diagnosis can be challenging due to its non-specificity and high sensitivity leading to significant number of false positives. However, it is an indispensable tool in diagnosing various systemic rheumatological conditions in combination with clinical judgement and further investigations.

Introduction

Antinuclear antibodies (ANA) are more commonly used in diagnosis of systemic rheumatological conditions. However, 2.9% of patients with significantly elevated ANA's with unexplained diagnosis were detected to have neoplasia [1]. It essential for patients with significantly elevated ANA titres to be investigated thoroughly to obtain a diagnosis, exclude potential life-threatening causes and to provide optimal patient management. One of the challenges faced with the use of ANA in diagnosis is because of its significantly high false positive results. The treating clinician should be mindful of its limitations to obtain an appropriate diagnosis. We report a case of a 59-year-old gentleman who presented with cardiac tamponade with persistently significant elevated ANA titres secondary to malignancy.

Case Report

A 59-year-old groundsman was referred for further investigation and management following an abnormal Computed Tomography (CT) scan done as an outpatient for investigation of scrotal swelling. He presented to his general practitioner (GP) with a one-week history

of scrotal swelling and heaviness further complicated by progressive dyspnoea, cough with purulent expectoration. In addition, he reported fatigue, arthralgia and 2-kilogram weight loss over the past month. He denies having any fever, chest pain, abdominal pain, urinary symptoms, night sweats, oral ulcers, skin rash, joint pain or swelling, testicular pain or penile discharge. His medical background includes childhood asthma and prior fractured femur requiring surgical correction. He is not on any regular medications and has no known allergies. He is a current smoker with a 40-pack year smoking history and social alcohol consumption.

On examination, he was dehydrated, afebrile with a respiratory rate of 16, SPO_2 of 99%, a heart rate of 80 and a blood pressure of 130/80. His cardiovascular examination showed soft dual heart sounds with no murmur. Auscultation of his lung fields revealed reduced air entry bibasally, more significantly on the left side. No crackles or added sounds were heard. His abdominal showed smooth non-tender mild hepatomegaly. No further organomegaly or abdominal mass were palpable and shifting dullness test was negative. His scrotal examination was unremarkable with minimal swelling, no skin changes and palpable symmetrical testis. He had no sacral or peripheral oedema. No skin lesions, oral ulcers, hair loss or stigmata of chronic liver disease were found.

His initial investigations showed a raised white cell count of 17.2 and plasma C-reactive protein (CRP) of 23 with normal amylase and lipase levels. His venous blood gas painted an uncompensated high anion gap metabolic acidosis picture. His ECG in Emergency Department (ED) showed low voltage QRS complexes at extremity and precordial leads (Figure 1). Urine chemistry and MCS were unremarkable. CT Chest, Abdomen and Pelvis (Figure 3) revealed a large pericardial effusion, bilateral pleural effusions, left mid zone consolidation and ascites. However, no liver lesions or intraabdominal masses were detected.

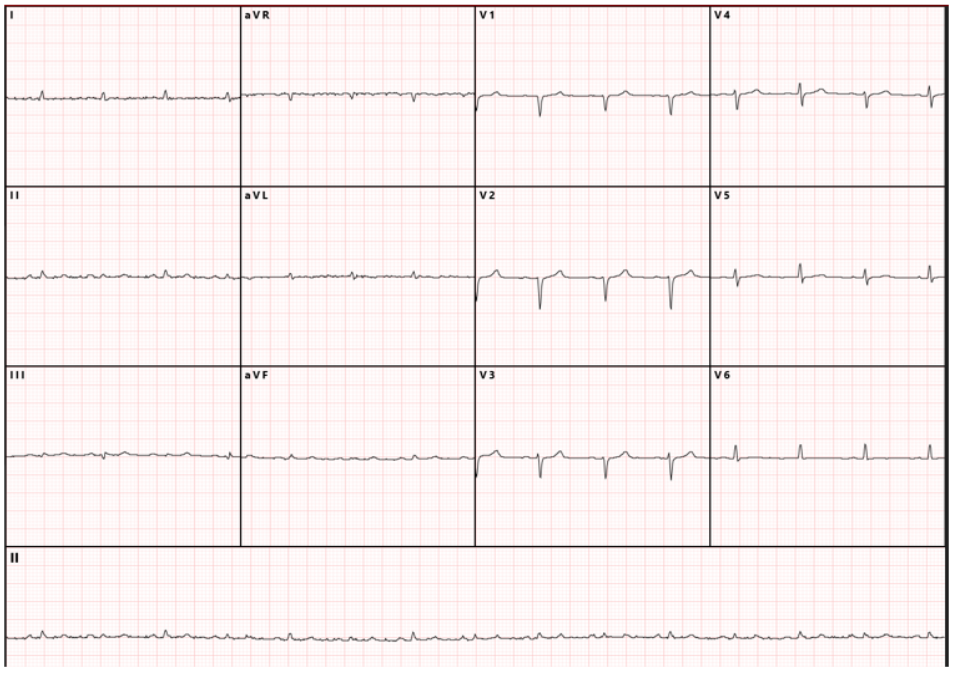

Figure 1: *ECG of the patient in the Emergency Department, 23/8/18 low voltage at extremity and precordial leads.*

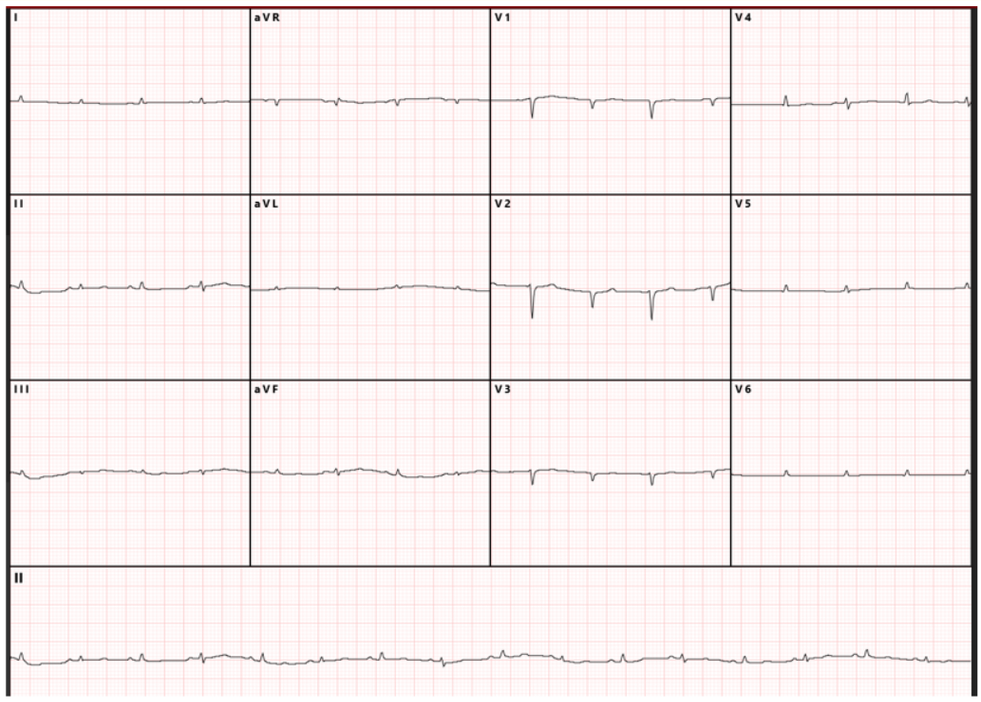

Figure 2: *ECG in Intensive Care Unit, 26/8/18, low voltage in limbs and precordial leads, prolonged QT interval.*

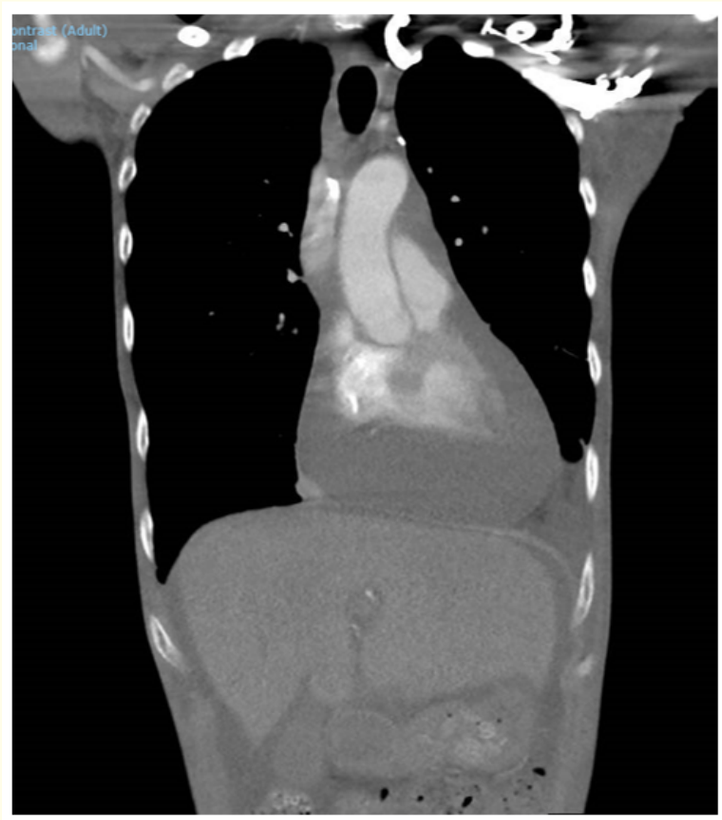

Figure 3: *CT Chest, Abdomen and Pelvis of the Patient.*

Further blood investigations including a rheumatology screen showed a mildly decrease C3 and C4 and a strongly positive ANA (1:2580) speckled appearance. Autoantibody testing for Anti-double stranded DNA antibody (anti-dsDNA), Anti-neutrophil cytoplasmic antibodies (ANCA), Anti-Sjogren Syndrome A (Anti-SSA(Ro)), Anti-Sjogren Syndrome B (Anti-SSA(La)), Anti-Ribonucleoprotein (Anti-RNP), Scleroderma Antibodies (Anti-Scl-70) and Anti-Histidyl Transfer RNA Synthase Antibodies (Anti-Jo-1) were negative. His blood cultures had no growth and his viral screen for Hepatitis A, B, C, Enterovirus, Adenovirus and Coxsackievirus were negative. Sexually transmitted infection screen for syphilis, gonorrhoea, chlamydia were also negative. However, he was positive for Cytomegalovirus (CMV) and Epstein-Barr Virus (EBV) IgM indicating previous exposure but IgG were negative. Apart from mildly elevated Carbohydrate Antigen 19-9 (CA19.9) and Carcinoembryonic Antigen(CEA), all other tumour markers were within normal parameters.

The next day, his condition deteriorated and was found to be hypoxic and hypotensive. He was transferred to the Intensive Care Unit (ICU) for Non-invasive ventilation (NIV) and consideration of ionotropic support. At this stage, the patient was found to be in heart failure with preserved ejection function (HFpEF) secondary to a cardiac tamponade, complicated with bilateral pleural effusion, ischaemic hepatitis, acute kidney injury, liver dysfunction and metabolic acidosis. Further ECG in ICU revealed low voltages in both precordial and limb leads as well as a prolonged QT-interval (Figure 2). A limited bedside echocardiogram was performed which revealed a large volume pericardial effusion and right ventricular wall hypokinesis suggestive of impending cardiac tamponade.

Left pleural drainage was performed for diagnostic and therapeutic purposes. A pericardial drain was inserted to relieve the cardiac tamponade and a total of 1.4 litres (L) of blood-stained pericardial fluid was drained. The pericardial fluid was analysed to be exudative while the pleural fluid was found to be transudative. Both pleural and pericardial effusion were negative for malignant cells found on cytology and had no growth on microscopy, culture and sensitivities (MCS) analysis. He was empirically commenced on Intravenous Tazocin 4.5g q8hourly for microbacterial coverage and prednisolone for suspected undifferentiated connective tissue disease in ICU.

Post-procedures, he showed significant clinical improvement. In the next three days he was transferred out from ICU to the medical wards. Subsequently over the next ten days he had increased exercise tolerance, mobility, appetite and his renal and liver functions gradually returned to baseline. He was discharged back home with oral prednisolone tapering and follow up with his local general practitioner (GP).

At follow up two months later, a repeat autoimmune screen was repeated which found persisting highly positive ANA (1:1280), speckled pattern but ENA screen were still negative. However, at four months post discharge, he represented to his GP with a painful lump at the right 10th rib (Figure 4). CT- Chest, Abdomen and Pelvis noted pleural base mass at the left lung base posteriorly with multiple enlarged mediastinal lymph nodes (Figure 5). Subsequently, Positron Emission Tomography (PET) scan showed multiple avidly hypermetabolic pulmonary nodules, lymphadenopathy and numerous bony hypermetabolic lesions consistent with metastases. Ultrasound guided tissue biopsy was positive for metastatic poorly differentiated squamous cell carcinoma and was referred to medical oncology and palliative care team for further management.

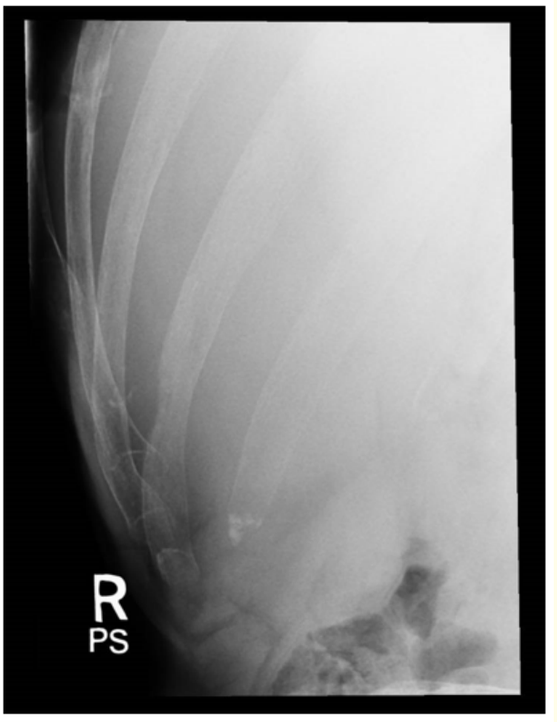

Figure 4: *Chest X-Ray, (19/12/18): There is an erosive lytic lesion involving the superior cortex of what appears to be the left 10th rib anteriorly.*

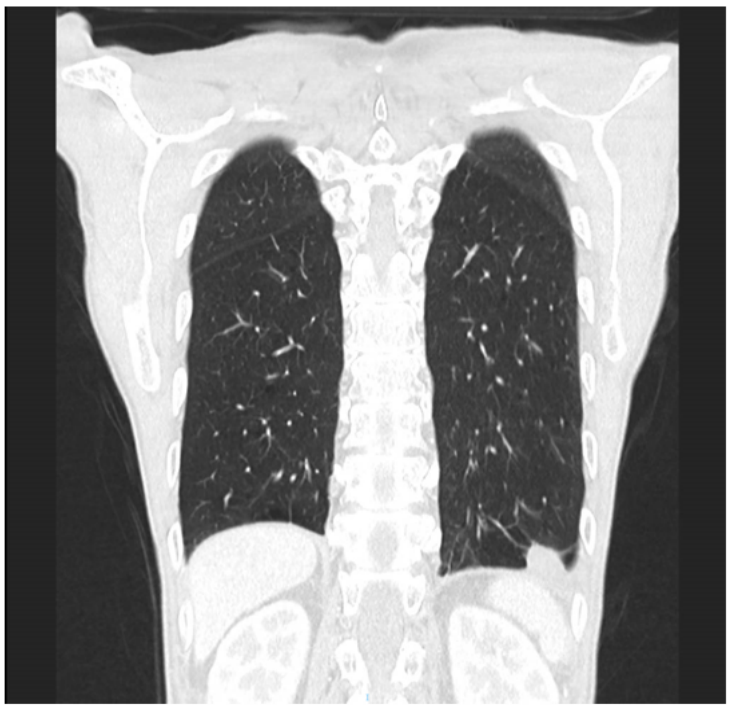

Figure 5: *CT Thorax, (20/12/18): Pleural base mass at left lung base posteriorly.*

Discussion

Antinuclear antibodies (ANA) refers to autoimmune antibodies produced against nuclear antigens. ANA is a common investigative tool for detecting rheumatic disease, more commonly systemic autoimmune diseases.

There are two main methods of measuring ANA; with both methods having its advantages and disadvantages. The first method of measuring ANA is using indirect immunofluorescence with human epidermoid carcinoma cell line (HEp-2). This is the commonest method use and is the gold standard recommendation by the American College of Rheumatology [2]. The HEp-2 cell has the large nuclei in different stages of the cell cycle and contains almost all clinically important nuclear antigens making it the most sensitive and can pick up almost all known antibodies against nuclear antigens [3]. This method also allows for reporting of staining patterns which significance will be discussed below. However, this method is costly and labour intensive as it requires highly trained technicians to read and interpret the results of the staining patterns [4].

ANA is commonly used as an adjunct to diagnose many systemic rheumatological diseases such as SLE, scleroderma, Sjogren's syndrome, juvenile idiopathic arthritis, polymyositis and dermatomyositis. However, a positive ANA is also associated with many other organ specific autoimmune diseases such as Hashimoto's thyroiditis, autoimmune hepatitis, primary biliary cirrhosis and many more. Viral and bacterial infections as well as malignancies can also be associated with high elevated ANA readings [2].

ANA results are reported in dilution titres and staining patterns. The cut off dilution titre remains debatable, as at this level, there is still a high level of false positives. A study by Mahler [5] demonstrated that titre levels of 1:40 will be found in up to 30% of healthy individuals. At this cut off, it will also detect 97% of patients with SLE, 100% of patients with systemic sclerosis and 84% of patients with

Sjogren syndrome [5]. The study also found that even at dilution level of 1:160, up to 5% of healthy individuals will have a false positive [5]. Similar findings were found by Abeles [6] and Marin [7]. A study by Abeles [6] found that less than 10% of individuals referred to a tertiary rheumatological clinic with titres of 1:160 were found to have a rheumatological disease. However, some studies have shown that autoantibodies can be found in individuals many years prior to first diagnosis of disease or symptom onset. In a study by Arbuckle [8], 78% of the participants with SLE has positive ANA titres (dilution of 1:120) before first diagnosis with a mean interval time of 3 years. This study implied that a positive autoantibody screen may predict future diagnosis of a rheumatological disease namely SLE.

Staining patterns refer to the appearance of the indirect immunofluorescence to autoantibodies have bounded to the HEp-2 cell. This is can be homogenous, speckled, centromere, nucleolar or peripheral pattern. The pattern of staining can suggest the implicated nuclear antibody involved based on usual location of the autoantigen. For example, the staining pattern implicated in limited systemic sclerosis is centromere appearance as there are autoantibodies directed against the centromere. The significance staining patterns is not sensitive and is loosely associated with autoimmune disease, as such further testing with solid assays would be required to determine the exact autoantibody is involved. Some have also suggested that staining patterns could also differentiate between true and false positive ANA results. A study by Mariz [9] of 256 participants found that a dense fine speckled pattern exclusively occurred in healthy individuals (i.e. false positives). The implication of staining patterns of the latter remains controversial as determining staining patterns is operator dependent and ANA positivity can occur up to 9 years prior to diagnosis of rheumatological disease [10].

ANA positivity has been long found in patients with malignancy. Some have suggested that a positive autoantibody may reflect immune reactivity to malignant cells [1,11]. One observational study showed in that in patients with chronic hepatitis infection, a proportion of them seroconverted to ANA positivity or increased ANA positivity months before hepatocellular carcinoma was detected [12]. ANA as a possible marker for malignancy or premalignancy marker has been long discussed in the past and found in many reviews that its positive significance is uncertain [1,11]. In our patient, the persistently high ANA titres were initially believed to be due to systemic rheumatological disease but as seen in studies, it is not uncommon that significantly high ANA titres can be found in patients with underlying neoplasia. It is an essential learning point that persistently significant high ANA titres should prompt a high index of suspicion and a thorough investigation is needed to obtain a diagnosis and commence appropriate treatment.

Conclusion

ANA is an important investigative tool in supporting the diagnosis of some rheumatological diseases. Positive ANA titres can be found in healthy individuals, individuals with malignancy and act as an indication of possible rheumatological disease development in the future. In addition, staining patterns may also suggest the type of rheumatological diseases involved. This case effectively highlights the significance of ANA as a tool in improving diagnosis efficiency but needs to be complemented by clinical judgement and further investigations to provide the optimal management for patients.

Bibliography

1. Madrid FF and Maroun MC. "Serologic Laboratory Findings in Malignancy". *Rheumatic Disease Clinics of North America* 37.4 (2011): 507-525.

2. Solomon DH., *et al*. "Evidence-based guidelines for the use of immunologic tests: antinuclear antibody testing". *Arthritis and Rheumatology* 47.4 (2002): 434-444.

3. Agmon-Levin N., *et al*. "International recommendations for the assessment of autoantibodies to cellular antigens referred to as antinuclear antibodies". *Annals of the Rheumatic Diseases* 73.1 (2014): 17-23.

4. Meroni PL and Schur PH. "ANA screening: an old test with new recommendations". *Annals of the Rheumatic Diseases* 69.8 (2010): 1420-1422.

5. Mahler M., *et al*. "Limited reliability of the indirect immunofluorescence technique for the detection of anti-Rib-P antibodies". *Arthritis Research and Therapy* 10.6 (2008): R131.

6. Abeles AM and Abeles M. "The clinical utility of a positive antinuclear antibody test result". *American Journal of Medicine* 126.4 (2013): 342-348.

7. Marin GG., *et al*. "Prevalence of Antinuclear Antibodies in 3 Groups of Healthy Individuals". *Journal of Clinical Rheumatology* 15.7 (2009): 325-329.

8. Arbuckle MR., *et al*. "Development of autoantibodies before the clinical onset of systemic lupus erythematosus". *New England Journal of Medicine* 349.16 (2003): 1526-1533.

9. Mariz HA., *et al*. "Pattern on the Antinuclear Antibody-HEp-2 Test Is a Critical Parameter for Discriminating Antinuclear Antibody-Positive Healthy Individuals and Patients With Autoimmune Rheumatic Diseases". *American College of Rheumatology* 63.1 (2011): 191-200.

10. Fritzler MJ. "The antinuclear antibody test: Last or lasting gasp?" *American College of Rheumatology* 63.1 (2011): 19-22.

11. Tan EM and Zhang J. "Autoantibodies to tumor-associated antigens: reporters from the immune system". *Immunological Reviews* 222 (2008): 328-340.

12. Imai H., *et al*. "Increasing titers and changing specificities of antinuclear antibodies in patients with chronic liver disease who develop hepatocellular carcinoma". *Cancer* 71.1 (1993): 26-35.

Volume 6 Issue 3 March 2019