Positivity of Anti-Proliferating Cell Nuclear Antigen (PCNA) Antibodies in Systemic Lupus Erythematosus (SLE): Case Series and Mini Review

Nur Diyana Mohd Shukri, Nurul Khaiza Yahya

ABSTRACT

**Background:** Autoantibodies to the proliferating cell nuclear antigen (PCNA) are rare autoantibodies and were previously believed to be specific biomarkers for systemic lupus erythematosus (SLE). However, recent studies have found that they occur in approximately 2-6% of patients with systemic lupus erythematosus and can be detected in other systemic autoimmune rheumatic diseases (SARD).

**Objective:** We report cases associated with positive anti-PCNA for a 10-year period starting from 2009 till 2018 and its role in the development of SLE.

**Methods:** We identified all patients with positive anti-PCNA antibodies and correlated these cases with the antinuclear antibody (ANA) test results.

**Results:** We described three cases of SLE with positive anti-PCNA antibodies. We concluded that anti-PCNA has low specificity for SLE.

**Conclusion:** Anti-PCNA in SLE cases might confer a more severe disease as most of the cases studied had severe renal and haematological involvement. Therefore, anti-PCNA in SLE cases would contribute to a more severe manifestation.

KEY WORDS
autoantibodies, proliferating cell nuclear antigen (PCNA), systemic lupus erythematosus (SLE), anti-nuclear antibodies (ANA), anti-dsDNA

INTRODUCTION

Antibodies targeting the Proliferating Cell Nuclear Antigen (PCNA) are considered as autoantibodies rarely detected in the human body. It is highly expressed in the rapidly proliferating cell nuclei of a variety of tissues and cell lines. It is mainly targeted against the 34 kDa protein that is part of the DNA polymerase delta multi-protein complex and plays an important role in DNA repair and replication. In our laboratory, anti-PCNA autoantibodies were detected using line immunoassay (LIA) which is a recent novel assay method.

We identified patients with positive anti-PCNA antibodies over a 10-year period from 2009 till 2018 and correlated the cases with the antinuclear antibody (ANA) testing done earlier. A total of seven patients with positive anti-PCNA antibodies were detected. These patients comprise of 1 case in 2014, 3 cases in 2017, and another 3 in 2018. We further described three cases of positive PCNA antibodies in systemic lupus erythematosus (SLE) cases. Hence, the aim of this study is to look into the significance of positive anti-PCNA cases in relation to SLE cases.

REPORT OF CASES

Case #1: SLE with lupus nephritis and Evan syndrome

The patient was a 25 year old Malay female, initially presented with gum bleeding and petechiae rash in 2017 and was diagnosed as Idiopathic Thrombocytopenic Purpura (ITP) with concomitant Iron Deficiency Anaemia requiring Haematology follow up. On further examination, it was noted that her ANA was positive with a titre of 1:320 and positive PCNA. Urine protein was positive 2+ to 3+ and urine 24-hour protein was 1.17 g. She was referred to the Rheumatology team in view of suspected Systemic Lupus Erythematosus (SLE). On further questioning, patient had on and off bilateral shoulder joint pain. There was no reduction in the range of movement or swelling, nor other joint involvement, cutaneous symptoms, oral ulcer or hair loss. She was therefore diagnosed as SLE with renal and haematological involvement (Evan syndrome). She was then referred to the nephrology team and was planned for an ultrasound on her kidney, ureter and bladder (KUB) and renal biopsy for staging. However, the ultrasound revealed both shrunken kidneys; the team was unable to proceed with the kidney biopsy due to the high risk of bleeding due to the underlying ITP with low platelet levels. Hence, the patient was assumed to have stage IV lupus nephritis due to her kidney size. The final diagnosis was SLE with stage IV lupus nephritis and Evan syndrome.

Case #2: SLE with lupus nephritis, Evan syndrome and anti-phospholipid syndrome

This was a 35 year old Malay female diagnosed with underlying SLE, lupus nephritis and Evan syndrome (predominant AIHA) for the past 14 years. She required haematology and rheumatology follow ups. She had multiple admissions due to recurrent relapses of SLE and autoimmune haemolytic anaemia (AIHA). She also developed secondary
antiphospholipid syndrome (APS) that was manifested by a left femoral vein deep vein thrombosis (DVT) in 2006 and recurrent foetal losses at 7 months and 2 months of pregnancy in 2005 and 2006. Besides that, she also had bilateral eye mature cataract that was possibly steroid-induced. During her latest relapse which was in December 2017, a connective tissue screening (CTD) was repeated and the PCNA was reported as positive.

Case #3: SLE with musculoskeletal involvement

This was a 15 year old Malay boy with underlying HaH disease and left testicular seminoma post left orchidectomy diagnosed since he was 5 months old. He was on regular follow up for his underlying medical illness. He was initially referred to the rheumatology team for having symmetrical bilateral hand joint pain for one month associated with swelling, morning stiffness and rashes over the forearm. Upon further investigation, the ANA results came back as positive and ENA was positive for Sm and Mi-2. He was diagnosed as SLE with musculoskeletal involvement.

DISCUSSION

We described three cases of SLE with positive anti-PCNA antibodies. The main purpose of this study is to look into the significance of positive anti-PCNA in relation to SLE cases. We also aim to highlight the severity of SLE cases with positive PCNA.

Anti-PCNA belongs to the extractable nuclear antigen (ENA) family. The incidence rate of patients with SLE is estimated to be about 2-6%\(^2\). To date, clinical relevance and significance of this issue is not very well understood. This is partly due to the low frequency of cases. Positivity of anti-PCNA in SLE cases is believed to be due to its role in DNA synthesis and repair. This, in turn, contributes to antinuclear activity with defective DNA repair in SLE patients\(^1\). Autoantibodies targeting PCNA were first described in 1976\(^2\). It was previously taught to be highly specific for SLE\(^1\). However, current studies have agreed that it has been described in a variety of systemic autoimmune rheumatic diseases (SARD), including patients with hepatitis B, hepatitis C virus infection and also malignancy\(^1\).

In the above cases, one patient was male while the other two were females, and all were aged from 15 to 35 years old. We described two cases of lupus nephritis with Evans syndrome and one case of SLE with musculoskeletal involvement. The Evans syndrome is a very rare autoimmune haemolytic anaemia (AIHA) and immune-mediated thrombocytopenia with no known underlying etiology. Most of the SLE patients with positive anti-PCNA have severe SLE complications with haematological together with renal involvement. This finding is in agreement with previous studies that associated positive anti-PCNA with a higher frequency of renal and haematological involvement such as thrombocytopenia and also central nervous system involvement\(^1\).

According to the ANA results, all three cases have positive anti-nuclear antibodies (ANA) results with predominantly homogenous pattern. Anti-nuclear antibodies are detected using an indirect immunofluorescence method and viewed using a fluorescent microscope. There are four major patterns of anti-nuclear antibodies which are homogenous, speckled, nucleolar and centromere. In this study, all SLE cases showed homogenous patterns with a high titre of 1: 320. This finding is in contrast with a recently published study\(^3\) where the most common ANA pattern among SLE patients is the speckled ANA pattern and a high ANA titre is not necessarily associated with SLE\(^3\). Besides that, two of the cases recorded other positive extractable nuclear autoantibodies (ENA) including antibodies towards nucleosome, histone, Sm, D1, Po, SS-A/ Ro 60 kD, SS-A/Ro 52 kD, SS-B/La, snRNP, Mi-2, PO/RP, and CENP-A/B. The cases show similarities in the ENA which are anti-Nucleosome, anti-Histone, anti-SmD1 and anti-U1-snRNP. The positivity to ENA might aid in the differentiation of different types of autoimmune rheumatic diseases as ENA usually precedes the clinical onset of disease and might be used as an early indicator of SLE\(^3\).

As for the anti-dsDNA antibody, the second and third cases showed positivity with readings with 183.91 IU/ml > 400 IU/ml respectively. The anti-dsDNA is considered as a gold standard in monitoring SLE’s disease activity. The titre is affected by the disease activity as shown by its rise, fall and fluctuations\(^4\). This is supported by a study by A.J. Swaak et al. who reported an increase of anti-dsDNA levels in patients undergoing disease exacerbation\(^4\). Additionally, it should be noted that the titre can disappear with treatment. Hence, it can be used as guidance in monitoring the immunosuppressive therapy to be given. A study by J. D. Reveille reported that those with a proliferative lesion on renal biopsy tend to have higher anti-dsDNA antibody levels due to better detection of anti-dsDNA in patients with renal problems\(^5\). This, in turn, contributes to a higher titre of anti-dsDNA in those with lupus nephritis.

CONCLUSION

In conclusion, we described three SLE cases from a total of seven positive anti-PCNA cases over a 10-year period. We concluded that anti-PCNA has low specificity for SLE. This is in agreement with a study by P. Vermeersch et al. who suggested that anti-PCNA has poor sensitivity for the diagnosis of SLE. However, positive anti-PCNA readings for SLE cases might confer a more severe disease as most of the identified cases had severe renal and haematological involvement. Therefore, anti-PCNA in SLE cases does contribute to a more severe manifestation.

REFERENCES