REVIEW ARTICLE

Antinuclear Antibodies in non-Systemic Autoimmune Rheumatic Disease Dermatological Conditions

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ABSTRACT

Antinuclear antibodies (ANA) indirect immunofluorescence assay (IFA) is the first line immunological investigation, mainly for systemic autoimmune rheumatic disease (SARD). However, ANA is also being requested in certain dermatological conditions particularly in those with immune dysregulation as underlying pathogenesis. It is not uncommon to get positive ANA results in patients with non-SARD dermatological conditions. However, the clinical significance and usefulness of ANA has not been well established. This review summarises the available studies on ANA IFA in non-SARD dermatological conditions which include atopic dermatitis (AD), psoriasis, vitiligo and autoimmune bullous diseases. It aims to determine the prevalence of ANA, the commonly reported ANA titres and patterns, as well as any clinical associations between ANA and non-SARD dermatological conditions.

Keywords: ANA, Atopic dermatitis, Psoriasis, Vitiligo, Autoimmune bullous diseases

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INTRODUCTION

Antinuclear antibody (ANA) testing is the primary assay for the detection of autoantibodies against nuclear antigens in serum or plasma samples. The indirect immunofluorescence assay (IFA) using human epithelial type 2 (HEp-2) cells as substrate is recommended and considered as the gold standard method for ANA detection. This technique allows the determination of two components of ANA which are the fluorescence intensity (titre) and staining patterns (1).

The serum screening dilution for ANA IFA varies between laboratories. The dilutions range between 1:40 – 1:160 with the majority opting for 1:80 as recommended by the latest 2019 European League Against Rheumatism/ American College of Rheumatology classification criteria for systemic lupus erythematosus (SLE) (2). The selected screening dilution frequently serves as the cut-off titre of positive ANA result in the respective laboratories. Depending on the ANA patterns identified, positive samples at the screening dilution are subjected to serial dilution. The reported titre is the final two-fold serial dilution of the sample that exhibits the presence of fluorescence in ANA IFA.

There are 29 ANA staining patterns on HEp-2 cells that have been identified by the International Consensus on ANA Patterns (ICAP) following a consensus of an international workshop in 2014 (3). According to ICAP, ANA patterns can be categorised into nuclear, mitotic and cytoplasmic. Despite multiple patterns being recognised, not all ANA patterns have similar levels of clinical relevance. Furthermore, not every immunology laboratory considers the 29 recognised patterns as being ANA positive findings and reports them (4).

ANA IFA is mainly carried out in cases suspected of systemic autoimmune rheumatic disease (SARD) such as SLE, rheumatoid arthritis, Sjogren syndrome, scleroderma, dermatomyositis and mixed connective tissue disease (MCTD) (5). A positive ANA result requires further tests to determine the presence of specific autoantibodies. The common subsequent tests to be performed are anti-dsDNA and anti-extractable nuclear antigens (ENA) antibodies which usually include anti-Smith, anti-Ro/ SS-A, anti-La/SS-B, anti-U1RNP, anti-Jo-1, anti-Scl-70 and anti-centromere antibodies (6,7). Combining inputs from ANA IFA and specific autoantibodies is considered as being the most informative by most clinicians and laboratory professionals (4).

ANA is a very useful test in SARD, especially SLE. According to the latest 2019 EULAR/ACR SLE classification criteria, ANA is the entry criteria for establishing the diagnosis of SLE. ANA IFA performed at 1:80 serum dilution is detected in 95% of SLE patients (2). ANA is also helpful in other SARD cases, especially those cases with suggestive clinical histories and other

supportive laboratory results. The presence of ANA has also been known to occur in certain other immune-related disorders such as autoimmune hepatitis, antiphospholipid syndrome and autoimmune thyroid diseases (7). However, ANA is not highly specific as it can be detected in non-autoimmune conditions including infections, malignancies and drug use (8). The presence of ANA has also been reported at low to moderate titres in healthy individuals, particularly in those aged more than 65 years old and in pregnant women (8,9).

Apart from the recommended and indicated testing, ANA is frequently being requested for many other conditions. This practice is particularly seen in suspected conditions with underlying immune dysregulations, even without any clear evidence on its clinical relevance. Among these disorders are dermatological conditions which are not associated with SARD such as atopic dermatitis (AD), psoriasis, vitiligo and autoimmune bullous diseases.

It is not uncommon to get positive ANA results in patients with non-SARD dermatological conditions. Positive ANA was reported during the initial phase of the diagnostic work-up, later on as the disease progresses or following certain treatments. Variable ANA concentrations have been reported, with most conditions showing low to moderate ANA titres. The commonly identified ANA patterns in non-SARD dermatological conditions are the typical patterns (homogenous, speckled and nucleolar) and their combinations. The ANA IFA findings in non-SARD dermatological conditions are summarised in Table I.

ATOPIC DERMATITIS

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterised by pruritic lesions and dry skin (10). It is commonly associated with personal or family history of atopy and elevated serum IgE level (10,11). The pathogenesis involves skin barrier dysfunction and type I hypersensitivity reaction. Autoimmunity has also been suggested to play a role in AD pathogenesis through elevated levels of IgE and IgG autoantibodies in AD patients (12). A few studies suggested that AD with

Table 1: Summary of ANA IFA prevalence, gender, titre and pattern in non-SARD dermatological conditions

	Prevalence	Gender	Titre	Pattern
AD	19% - 40.6% of overall AD (13-15, 20-21) 2.6% - 14% of paediatric AD, age range 0.5 – 18.8 years (17-19)	47.4% - 71.4% female (13-14, 20) Female > male (Odds ratio 3.5) (19)	Low to moderate 1:40 – 1:640 (13-14, 18-20)	Common pattern(s): - Speckled (14.3% - 78.3%) - Homogenous (13.0% - 67.9%) - Mixed homogenous/speckled (19.2% - 36.8%) (13-14, 17, 19-20) Other pattern(s): - Mixed speckled/nucleolar (13) - Mixed speckled/other patterns (13) - Nucleolar (19, 20) - Few nuclear dots (19) - PCNA (20) - DFS (21)
Psoriasis	1.7% - 49.5% of psoriasis (27, 30, 32-35) 14% - 57% of PsA (28-29, 30, 34) 40% - 75% became ANA (+) after infliximab (32-35)	60% female with psoriasis (27) 47.9% - 75% female with PsA (28-29)	Low to moderate 1:80 – 1:640 (27, 29-30)	Common pattern(s): - Speckled (17% - 95%) - Homogenous (18% - 60%) - Nucleolar (24% - 42.6%) (27-28, 30, 33) Other pattern(s): - Mixed speckled/nucleolar (28) - RLM (30) - Nuclear dots (30) - Centrioles (30) - Mitotic spindle (30)
Vitiligo	2.9% - 3.8% (tissue substrates) (43-45) 12.4% - 57.1% (HEp-2 cells) (46-48, 51-52) 8.9% of paediatric vitiligo, age range 2 – 17 years (49)	57.1% - 90% female (47-48, 51)	Low to moderate < 1:320 (48)	Common pattern(s): - Speckled (49.1% - 56.7%) - Homogenous (49.1%) - Nucleolar (36.7%) (48, 50)
AIBD (PV)	37.3% - 40% of PV (55-56)	80% females with PV (56)	Low to moderate 1:160 – 320 (55-56)	Common pattern(s): - Speckled (45%) - Homogenous (9% - 50%) - Mixed homogenous/speckled (5% - 22.7%) - Midbody (22.7%) - Nucleolar (13.6%) (55-56) Other pattern(s): - Centromere - Centrosome (55)

AD: atopic dermatitis; PsA: psoriatic arthritis; AIBD: autoimmune bullous diseases; PV: pemphigus vulgaris; DFS: dense fine speckled; PCNA: proliferating cell nuclear antigen; RLM: rim like membranous

positive ANA is a subgroup of AD which may benefit from an autoimmunity management approach (12,13).

Prevalence and Clinical Associations

ANA testing is not routinely carried out in AD but it has been found to be present in some patients with AD. It is useful for excluding SLE particularly in female patients with facial dermatitis and photosensitivity (14). Several studies in Japan showed the presence of ANA in patients with AD (13–15). Tada et al. reported positive ANA with titres between 1:40 - 1:640 in 25.5% of 89 AD patients. However, these findings were not statistically significant when compared to the control group (14). This was in contrast to an earlier study where ANA positivity was statistically significant in 26.3% of 57 AD patients with facial lesions as compared to the controls (15). A more recent study again in Japan also showed a significant ANA positivity (titre 1:40 - 1:640) in 19% of 100 AD patients. In addition, ANA positivity was found to be significantly associated with photosensitivity among the male patients (13). A systematic review of eight studies involving 1045 AD patients and 1273 controls concluded that ANA was significantly more prevalent in AD. However, there was no association between ANA and the severity of AD (16). Similar findings were also seen in studies of AD with facial involvement where the ANA positivity rate was higher compared to the controls but it did not correlate with the disease severity (13,15).

Atopic Dermatitis in Children

Although it can occur at any age, AD is more prevalent in children (11). A few studies were conducted to determine ANA positivity among children with AD aged less than 18 years (17–19). Studies among 72 children with AD in Hungary showed about 14% of them were ANA positive (18). A cross-sectional study among 346 children with active AD in Estonia found ANA positivity in 8% of them at a cut-off titre of 1:40 (19). Both studies concluded that there was no significant difference in the ANA positivity rate between the AD and the control groups (18,19). Another study in India found a lower rate of ANA positivity among children with AD. A low titre of ANA of 1:40 was detected in only 2 of the 76 (2.6%) children tested. Both of them were female with moderate facial involvement and photosensitivity (17). However, in that study, acetone-fixed rat liver was used as a substrate rather than the standard use of HEp-2 cells as in the other studies for detecting ANA. Hence, Dhar et al. concluded that ANA was not a feature of AD among children in North India (17).

Titres, Patterns and Specific Autoantibodies

Generally, ANA tires in AD were between low to moderate (1:40 - 1:640) (13,14,19). Higher titres of ANA were more commonly found in females than in males with AD, but no significant difference had been reported (19,20). Common ANA patterns seen in AD were speckled, homogenous, DFS and mixed speckled/homogenous (13,14,19–21). Other less common patterns included nucleolar, few nuclear dots, proliferating cell nuclear antigen (PCNA) and mixed speckled/other patterns (13,19,20). However, SARD suggestive symptoms and specific antibodies such as anti-dsDNA, anti-SSA/Ro, anti-SSB/La (13,14), anti-Smith and anti-RNP (20) were not detected in AD patients with positive ANA.

On the other hand, anti-DFS autoantibodies that are rarely associated with SARD were detected in ANA-positive AD patients. Anti-DFS were seen in nearly 30% of Japanese with AD, suggesting the possibility of an anti-DFS-positive AD subset. Apart from AD, anti-DFS were also detected in patients with asthma and interstitial cystitis (21). However, it is still unclear whether anti-DFS has a role in AD immunopathogenesis (21,22).

PSORIASIS

Psoriasis is a chronic inflammatory skin disease with systemic involvement (23). Its pathophysiology is a complex cellular immune reaction mainly involving T lymphocytes, macrophages and T helper 17 cytokines such as interleukin (IL)-17, IL-23 and tumour necrosis factor (TNF) (24,25).

Prevalence

The laboratory findings in psoriasis are non-specific and autoantibodies including ANA have also been reported (26,27). ANA measured using ELISA was positive in 20 (17%) of 118 patients with psoriasis in a cross-sectional study conducted in India. It was mainly seen in plaque psoriasis (80%) and did not show gender predilection (26). Another study in Bangkok, Thailand demonstrated positive ANA IFA in only five out of 300 (1.7%) patients with psoriasis. The reported ANA titres were between 1:80 to 1:640 with patterns of either homogenous or speckled (27).

Psoriatic Arthritis

Many studies were conducted which determined ANA in psoriasis with specific involvements particularly, psoriatic arthritis (PsA). Silvy et al. reported that ANA IFA was positive in 57% of 232 PsA at a cut-off titre of 1:100. It was detected more frequently in women (62%) with the majority (95%) of patients demonstrating constant speckled patterns (28). The remaining positive ANA (5%) showed mixed nucleolar/speckled patterns. None of the ANA positive patients had clinical features of SLE or its associated autoantibodies i.e., anti-dsDNA, anti-Sm, anti-SSB/La and anti-RNP (28). Another study reported a lower prevalence of ANA IFA among patients with PsA. ANA IFA at the cut-off titre of 1:80 was seen in only 13 out of 94 patients (14%) and this was not statistically significant compared to the ANA-negative PsA patients. This study however did not report the ANA titre and patterns (29).

Titres and Patterns

A recent study in Greece found that ANA IFA was detected in about half, (50/101) of psoriasis and (47/100) of PsA patients at a cut-off titre of 1:80. More than 80% of them demonstrated low ANA titres of between 1:80 to 1:320 (30). Several ANA patterns were identified but the commonest were speckled, nucleolar and homogenous. Further testing of these 97 ANA positive samples showed that the most common autoantibody specificity among psoriasis and PsA patients was against DFS70 (11.3%) (30). However, 69 out of 97 (71.1%) of the ANA positive samples did not demonstrate autoantibody specificity against the tested 23 extractable nuclear antigens. Anti-DFS70 was shown to be significantly correlated with the female gender as well as with lower psoriasis area and severity index (PASI) score in psoriasis. In PsA, anti-DFS70 was significantly correlated with lower C-reactive protein levels and inflammation of the tendon or ligament at bony insertion sites (30).

Treatment with Biologic Agents

Several studies have also looked into ANA status in patients with psoriasis following treatment with biologic agents (31–36). Between 40-75% of patients with psoriasis became ANA positive after being treated with infliximab, an anti-TNF alpha (32–35). This significant finding was found in as early as 22 weeks following infliximab commencement among 25 patients with severe recalcitrant psoriasis (32). Another observation found that 55% of previously ANA-negative PsA patients (n=34) became positive after 4-5 years, while all 14 patients remained ANA positive with anti-TNF alpha therapy. Increases in ANA titres were also observed in some patients following treatment (28,33,36). The commonly identified ANA patterns following anti-TNF alpha in psoriasis were homogenous, speckled and nucleolar (32,33). On the contrary, antibody evaluation in four patients with psoriasis found that their ANA levels decreased in a time-dependent manner following treatment with secukinumab (30). Secukinumab is a biologic agent that acts as an inhibitor of the IL-17 pathway (37). It has a different mechanism of action from infliximab and other anti-TNF alpha described in the previously mentioned studies (38).

Clinical Associations

Clinically, none of the studies found correlation between becoming ANA positive following biologic agent and lupus-like syndrome, SLE or other autoimmune conditions among patients with psoriasis (28,33–35). Faster clinical response to infliximab was seen in patients who developed ANA during therapy as indicated by faster decrease in the PASI score (33). Another study, on the other hand demonstrated that higher baseline ANA titre was significantly associated with higher risk of development of anti-infliximab and loss of response to infliximab (36). Development of ANA during anti-TNF alpha therapy was also suggested as an indicator for potential treatment failure (39).

VITILIGO

Vitiligo is characterised by well-demarcated skin depigmentation due to loss of melanocytes. Multiple aetiopathogenesis of melanocyte destruction had been proposed including autoimmune and neural theories (40). Vitiligo had also been associated with other autoimmune disorders particularly autoimmune thyroid diseases (41,42). Due to this association, several studies had investigated ANA and its possible roles in vitiligo.

Prevalence

Inconsistent reports of ANA prevalence in patients with vitiligo were published, ranging from as low as 2.9% to as high as 35.3% (43–47). Low ANA prevalence among patients with vitiligo were seen in studies conducted in early 1980s where tissue substrates were used for ANA IFA (43–45). The use of tissue substrate is known to be less sensitive and specific for the detection of ANA. A meta-analysis involving eight studies with 905 Asian and Caucasian patients with vitiligo found that ANA prevalence was 12.5% (46). They also reported that ANA prevalence was higher in the Caucasian patients with vitiligo (16.3%) compared to their Asian counterparts (11.2%). ANA positivity was significantly more prevalent in patients with vitiligo compared to healthy controls (46,47).

Titres and Patterns

In most patients with vitiligo, the ANA titres were low to moderate (less than 1:320) (48,49). Two studies conducted in different hospitals in Bangkok in 2017 (50) and 2020 (48) found that the speckled pattern was seen in about half of ANA-positive patients with vitiligo. The other patterns identified included nucleolar and homogenous (48,50).

Clinical Associations

Several factors had been identified to be significantly associated with positive ANA in patients with vitiligo. They included female gender, presence of anti-thyroglobulin (48), disease duration longer than one year (47) and lesions involving the hands and arms (50). Although non-segmental vitiligo was said to be associated with autoimmune aetiology, ANA was not shown to be associated with this type of vitiligo (47,48). Interestingly, vitiligo patients with autoimmune thyroiditis were found to have significantly smaller thyroid volume if ANA was present (51).

Subsequent specific autoantibody testing such as anti-dsDNA following ANA-positive results in adult patients with vitiligo was rarely positive (51). However, anti-dsDNA and anti-ENA positivity was found in 4.2% of 145 paediatric patients with vitiligo in China although it was not statistically significant when compared to the control group. In addition, none of the paediatric participants were diagnosed with SARD (49). Most of the studies found no concomitant SARD particularly

SLE in vitiligo patients with positive ANA (48,50). It was concluded that even though ANA positivity was more frequently seen in patients with vitiligo, ANA was neither involved in the pathogenesis nor a predictor of SLE or other SARD in these patients (46,52).

AUTOIMMUNE BULLOUS DISEASES

Autoimmune bullous diseases (AIBD) are characterised by the presence of dermal blisters with circulating autoantibodies. They include pemphigus vulgaris (PV), bullous pemphigoid (BP), linear IgA dermatosis and dermatitis herpetiformis (53,54). The publications on ANA in AIBD are scarce and limited to PV.

Prevalence

Two studies investigated the presence of non-specific autoantibodies including ANA in patients with PV (55,56). The first study was published by Blondin et al. in 2009. It was carried out among 59 patients with PV and 50 healthy blood donors in a medical centre in Calgary, Canada. ANA was detected in 37.3% of the patients with PV and the positivity was statistically significant compared to the healthy controls (55). A more recent study was conducted among 50 Egyptians with PV and 50 controls. ANA was significantly detected in 40% of the patients and was more commonly seen in females (80%) (56). Both studies found that ANA was present in more than one-third of patients with PV. The discrepancy might be contributed by the different types of substrates used (HEp-2000 vs HEp-2 cells) and the cut-off titre (1:160 vs 1:100).

Titres and Patterns

Most patients with PV exhibited low to moderate ANA titres (1:160-1:320) (55,56). Higher ANA titres were usually seen in patients with concomitant autoimmune disease such as SLE (55). The most common pattern identified was speckled followed by mixed speckled/homogenous and midbody patterns (56).

Clinical Associations

PV may occur in association with other autoimmune diseases including myasthenia gravis, thymoma and SARD (57). The presence of ANA in patients with PV, similar to the general population may precede the clinical manifestations of autoimmune diseases particularly SLE (58,59). Although no significant difference in ANA positivity between treated and untreated PV was found (56), treatment of PV which included corticosteroids and immunomodulatory agents might have affected ANA production, thus lowering the detection rate. Subsequent anti-dsDNA and ENA tests by Blondin et al. among ANA-positive patients with PV were negative except in one patient with SLE who was positive for anti-Ro and anti-La antibodies (55). To date, it had not been determined whether ANA has pathogenic or clinical roles in PV. However, it was recommended that ANA-positive patients with PV be closely monitored for the development of concomitant autoimmune disease (56).

LIMITATION

Several factors such as slide preparation technique, types of substrates, variation in the commercially available kits and different cut-off values may influence the ANA IFA results. Apart from these, there is subjectivity in ANA interpretation as it is undeniably operator dependant. The use of HEp-2 cells and its equivalent as substrates was only available after 1975 (6). Studies prior to that era used animal tissue substrates (44,45) which were inferior to HEp-2 in term of sensitivity (6). ANA cut-off values were not the same among studies. In this review, titre of 1:40 (14,17) and above were considered as positive. The reported ANA patterns varied among studies but not all presented this information. There was also a high probability that non-typical ANA patterns missed to be identified as they were not being routinely reported by the laboratory. The same goes to the relatively newly identified patterns such as DFS for which autoantibodies and target antigens were only fully characterised in the late 1990s (60).

CONCLUSION

In conclusion, although ANA was more commonly detected in atopic dermatitis, psoriasis, vitiligo and autoimmune bullous diseases, it was not shown to be a useful marker in establishing the diagnosis, types and severity. The usual findings were ANA of low to moderate titres with typical patterns of speckled, homogenous, nucleolar or mixed speckled/homogenous. However, the presence of ANA in these patients was not associated with SARD including SLE. In psoriasis, ANA may be a potential biomarker for biologic agent treatment response.

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