EDITORIAL

Antinuclear Antibodies: Historical Insights for Current Understanding

The first report of antinuclear antibodies (ANA) was in 1948 by Hargraves *et al.* at the Mayo Clinic (1). ANA were found to be part of the Lupus Erythematosus-cell (LE-cell) phenomenon, which involved nuclei adhesion and phagocytizing denatured nuclear material of cells by immature myeloid cells in the bone marrow of Systemic Lupus Erythematosus (SLE) patients (2). In the 1950s, Indirect Immunofluorescence assay (IIF) was described, initially on cryopreserved sections of rodent tissues and was employed for ANA screening for about two decades. In the 1970s, human tissue culture cells, mainly human epithelial type-2 cells (HEp-2 cells), were developed. These laryngeal carcinoma derived cells were more efficient due to their easier productibility, bigger nuclei, and the fact that they expressed antigens in various stages of the cell cycle thus increasing the sensitivity of this technique (3). The discovery of ANA marked a new era for autoimmunity, leading to the identification of many new antibodies that couldn't be detected with the older substrate. As a result, new clinico-immunological entities emerged, leading to the definition of new systemic auto-immune diseases other than SLE. In recent years, new semi and fully automated detection methods, such as enzyme-linked immunosorbent assay (ELISA), Line/dot blot and electro-chemiluminescence (ECLIA), have been developed to homogenize testing results and minimize bias related to inter-observer variability. This has led to new conclusions regarding ANA performance in diagnosing rheumatic diseases with the definition of new disease specific auto-antibodies.

Not only that, large observational studies using these novel biomarkers allowed better understanding of each rheumatic disease, and dividing it into clinico-immunological clusters. In fact, some auto-antibodies showed to correlate with specific clinical features, disease progression, and even response to treatment. A great example is Systemic Sclerosis (SSc). Anti-Topoisomerase I SSc patients seem to have different organ damage than anti-

centromeres patients. While the first have more fibrotic features such as skin sclerosis and interstitial lung fibrosis, the latter have higher risk for vasculopathic manifestations such as pulmonary hypertension and telangiectasias. Besides, these novel biomarkers can be more practical for clinicians because of their quick results and better specificity. In fact, ANA detection with IIF proved to miss them. Two major examples are Sjogren Syndrome and antisynthetase syndrome with anti-SSA/Ro60 and anti-Jo 1 antibodies that can be missed as staining is usually cytoplasmic.

Thus said, the gold standard for ANA screening still remains IIF on Hep-2 cells (2). Therefore, ANA testing results should be interpreted with caution, taking into consideration factors such as titers, IIF aspect and clinical data. In fact, ANAs proved to be present in patients with non autoimmune diseases, such as neoplasms, infectious diseases, and even in healthy individuals. Only effective communication between clinicians and biologists can sometimes solve an interpretation issue. A great example is anti-PCNA staining on IIF. While this pattern is usually highly suggestive of SLE with anti-PCNA antibodies, it can also be indicative of an active neoplasm that needs to be confirmed by a totally different diagnostic strategy. A recent Tunisian study suggested a gap in the training of internal medicine residents regarding the screening techniques and interpretation of IIF results (4). Moreover, variations in the daily practice of testing for ANAs in medical laboratories in Tunisia have been reported (5).

To address this issue, a learning exercise for both biologists and clinicians was initiated by TAYI in collaboration with RTBC in order to improve diagnostic and therapeutic management of connective tissue patients. This initiative was entitled «Autoantibodies: the mystery revealed». It brings together young internists and immunologists with a common goal: jointly producing mental maps. The project aims to encourage dialogue and cooperation between the two specialties. It resulted in the production of thirty-nine mental maps for the ANA most frequently encountered in routine practice covering thirty-six different antibodies, providing crucial "need-to-know" information, including biological characteristics and clinical correlations. Each map was produced by a pair composed of two residents (internist and immunologist) and supervised by two seniors (internist and

immunologist). This project focuses on connective tissue diseases, which are among the most common systemic autoimmune diseases.

To be continued...

Houssem Abida, MD
President, TAYI

References:

1. Hargraves M M, Richmond H, Morton R. Presentation of two bone marrow elements; the tart cell and the L.E. cell. Proc Staff Meet Mayo Clin. 1948;23(2):25-8.
2. Ahsan H. Origins and history of autoimmunity: A brief review. Rheumatol Autoimmun. 2023;03(01):9-14.
3. Irure-Ventura J, López-Hoyos M. The Past, Present, and Future in Antinuclear Antibodies (ANA). Diagnostics. 2022;12(3):647.
4. Toujani S, Laamari H, Ben Yahya W, Abdelkefi C, Meddeb Z, Larbi T *et al.* La recherche et l'interprétation des anticorps antinucléaires : évaluation des connaissances des résidents en médecine interne en Tunisie. Rev Médecine Interne. 2022;43:A426.
5. Zamali I, Korbi F, Bousseta S, Ben Hmid A, Samoud S, Galai Y *et al*. Pratique actuelle des laboratoires d'analyses médicales pour le dépistage des anticorps anti-nucléaires en Tunisie. *Revue Tunisienne De Biologie Clinique*. 2023;*30*(3)

Steering Committee

Scientific Committee - Immunologists

Mariam Ghozzi
Clinical immunology department, Farhat Hached University Hospital, Sousse, Tunisia
Faculty of Pharmacy of Monastir, Monastir university

Amène Ben Bnina
Hematology department, Sahloul University Hospital, Sousse, Tunisia
Faculty of Pharmacy of Monastir, Monastir university

Ameni Jerbi
Clinical immunology department, Habib Bourguiba University Hospital, Sfax, Tunisia Faculty of medicine of Sfax, Sfax University

Sabrina Mejdoub
Clinical immunology department, Habib Bourguiba University Hospital, Sfax, Tunisia Faculty of medicine of Sfax, Sfax University

Mourad El Ghali
Clinical immunology department, Fattouma Bourguiba University Hospital, Monastir, Tunisia Faculty of medicine of Monastir, Monastir University

Imen Ayadi
Clinical immunology department, La Rabta University Hospital, Tunis, Tunisia
Faculty of medicine of Tunis, Tunis El Manar University

Wiem Lazzem
Clinical immunology department, Habib Thameur University Hospital, Tunis, Tunisia
Faculty of Pharmacy of Monastir, Monastir university

Mariem Ben Ahmed
Clinical immunology laboratory, faculty of medicine of Sousse, Sousse, Tunisia
Faculty of medicine of Sousse, Sousse University

Maha Changuel
Clinical immunology department, Fattouma Bourguiba University Hospital, Monastir, Tunisia
Faculty of Pharmacy of Monastir, Monastir university

Scientific Committee - Internists

Imen Ben Hassine
Internal medicine department, Sahloul University Hospital, Sousse, Tunisia
Faculty of medicine of Sousse, Sousse University

Rim Bourguiba
Internal medicine department, Interior Security Forces Hospital, Tunis, Tunisia
Faculty of medicine of Tunis, Tunis El Manar University

Wafa Skouri
Internal medicine Department, Taher Maamouri Hospital, Nabeul, Tunisia
Faculty of medicine of Tunis, Tunis El Manar University

Wafa Baya
Internal medicine department, Sahloul University Hospital, Sousse, Tunisia
Faculty of medicine of Sousse, Sousse University