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Research Paper

Anti-centromere antibodies and clinical confrontation

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ABSTRACT: *Introduction: Anti-centromere antibodies (ACAs) are a variety of anti-nuclear autoantibodies (ANAs) directed against different kinetochore proteins. They are detected on HEp2 substrates by the immunofluorescence technique (IIF). They are found during several autoimmune diseases (AIDs), frequently during localized Scleroderma. The aim of this study is to retrospectively analyze from serums containing ACAs, the pathologies associated with them.*
Materials and methods: The study was carried out at the Department of Immunology, Central Laboratory of Medical Analyses, Hassan II University Hospital of Fez during a period of 3 years. All the serums addressed for ACAs screening were included. The indirect immunofluorescence (IIF)was used for ANAs screening and the Immunodot for the identification of antigenic specificities according to the manufacturer's instructions.
Results: Out of sixty-four sera studied, eleven ACAs positive sera were found. The average age was 50 years±18. A female predominance (81.8%) was observed with a sex F/H ratio of 4,5. Anti-nuclear antibodies were positive in all cases, with a centromeric pattern in 9 cases and a speckled pattern in 2 cases, the titer was between 1/160 to 1/1280. Antigenic identification by Immunodot showed that: the two antigenic specificities CENP-A and CENP-B were found in 5 cases, isolated CENP-B specificity was identified in 4 cases, and CENP-A-B was observed in 2 cases. Results from our study also identified the association between ACAs and Scleroderma a significant association of ACAs with Scleroderma (45%).
Conclusion: The presence of ACAs may be associated with several AIDs, primarily scleroderma. These autoantibodies are an important marker for diagnosis/prognosis of autoimmune diseases.
KEY WORDS: *Anti-centromere antibodies, Autoimmune diseases, Scleroderma.*

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I. INTRODUCTION

Anti-centromere antibodies (ACAs) represent a variety of anti-nuclear antibodies (ANAs) directed against different kinetochore proteins. They are evidenced by the technique of indirect immunofluorescence (IIF) on HEp-2 cells [1,2]. AACs can occur in several autoimmune diseases (AIDs), most commonly in scleroderma [3].
The current study evaluates the association with AACs and disease.

II. MATERIALS AND METHODS

The study was carried out in the Department of Immunology, Central Laboratory of Medical Analyses, Hassan II University Hospital of Fez during a period of 3 years.

All the serums samples addressed for ACAs screening were included. The techniques were used were indirect immunofluorescence (first-line) for ANAs screening, and Immunodot (second-line) for the identification of antigenic specificities of ACAs. The data was collected and entered into an EXCEL file

III. RESULTS

Out of sixty-four sera studied, eleven ACAs positive sera were found. The average age was 50 years±18.6. A female predominance (72,7%) was observed with a sex ratio F/M of 4.5 (Table 1).

Table 1: Distribution of patients by sex.

	Number	Percentage
Female	9	81,8%
Man	3	18,2%

In our series, eleven sera tested were positive for ACAs.

In the patients with positive ACAs, the ANA's screening at IIF objectified the presence of the centromeric pattern in 82,8% and speckled pattern in 27,2% of cases. The titer varied between 1/160 to 1/1280 (Table 2) .

Table 2: Distribution of patients based on ANAs results observed at IIF.

		Centromeric pattern	Speckled pattern
Titer	1/160	5	0
	1/320	2	2
	1/640	1	0
	> 1/1280	0	1

Antigenic identification by Immunodot showed that both specificities CENP-A and CENP-B were found in 5 cases, CENP-B specificity isolated was identified in 4 cases, and CENP-A-B was found in 2 cases (**Table).**

Table 3 : Distribution of patients based on Immunodot identification results

Specificity	CENP A and CENP B	CENP B	CENP A/B
Number of cases	5	4	2

Results by clinical table showed an association of positive ACAs with Scleroderma (45%), and Lupus (36%). **(Table 5).**

Table 5 : Distribution of patients by clinical table.

Pathology	Scleroderma	Systemic lupus	Rheumatologic disease
Number of cases	5	4	2

IV. DISCUSSION

This study focused on the retrospective analysis of ACAs positive serums and their clinical associations. The result showed a female predominance (81.8%), with a wide age range, these clinical characteristics are in agree with those obtained by Tsukamoto and al. in a study of 585 cases [3]. In accordance with the average age observed in our series, a study by Respaldiza and al. showed the positivity of the ACAs in all women having a systemic lupus erythematous with a median age of 47.5 years [4].

The clinical utility of anti-centromeric antibodies was first described in 1961 [8]. Nearly 20 years later, serum producing a subset of this staining pattern was identified at the centromere of chromosomes and thereby named anti-centromeric antibodies (ACAs). Subsequent studies of this pattern led to the discovery of three proteins, the first centromeric proteins in any species (CENP-A, CENP-B, and CENP-C). The reader is referred to an essay by William Earnshaw for a detailed overview regarding the discovery and molecular characterization of these proteins [9].

The distinctness and ubiquitous nature of the ACAs staining pattern maintains its continued utility, even after the discovery of numerous other centromeric proteins [11-13]. A recent effort by the International Consensus on Anti-Nuclear Antibody Patterns (ICAP) to clarify clinical associations between IIF staining patterns and disease states concluded that all patterns should be "confirmed by antigen-specific immunoassays, except for the ACAs pattern [14].

The ANAs results observed in our series showed that the group of patients with centromeric pattern and ANAs titer of 1/160 was the most important. While, Feki et al. in a retrospective study of 90 patient report the titer of 1/320 as the most abundant [6]. The titer of ANAs is important, a relation between high titers and the presence of AIDs has been noted in the literature. ACAs pattern on HEp2 cells appeared as a specific fluorescence consisting of 30 to 40 regular grains dispersed over the nuclei of cells in interphase or division by grouping around the mitotic spindle [3].

The result obtained in our series showed an association of positive ACAs and systemic Scleroderma (45%). The prevalence of ACAs in AIDs varies from one series to another, it is all the higher the more in CREST syndrome (57-82%) [9]. In fact, these antibodies are an important diagnostic value in CREST Syndrome. While, its significance in Primary Sjögren's syndrome remains to be clarified precisely by Nakamura et al. [16]. Moreover, a study by Tramposch and al. showed that the presence of ACAs is a marker of CREST syndrome, but they may also be found for a prolonged periods of time in patients with connective tissue diseases. And they may be of value in predicting in future development of the CREST Syndrome in patient with isolated myositis or Raynaud's phenomenon [**15**]

V. CONCLUSION

The presence of ACAs may be associated with several auto immune diseases, mainly systemic scleroderma in its minimal form (CREST syndrome). The establishment of an individual immunoprofile is an important marker for diagnosis/prognosis of autoimmune diseases.

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