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RESPONSE LETTER TO THE EDITOR

Antinuclear antibodies in COVID 19

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We appreciated very much the interesting study by Chang et al.[1] on the presence of antinuclear antibodies (ANAs) in patients with moderate/critical coronavirus disease 2019 (COVID 19).

Both we and Chang and collaborators described the presence and significance of ANAs in patients with COVID-19. The two experiences can be compared because Chang et al. studied a number of cases only slightly larger than us. In our opinion, the most important finding is represented by the presence of the nucleolar ANA reactivity, which, in the study by Chang et al.,[1] as in ours,[2] is the most frequently detected among the different ANA patterns. In this regard, it is worth mentioning that the nucleolar ANA pattern is one of the several ANA pattern detectable by Indirect immunofluorescence (Figure 1), together with other patterns, such as speckled, homogenous, multiple nuclear dots, and rim like membranous; this pattern can be the serological marker of systemic sclerosis and its antigenic target is the topoisomerase I protein (or scl70). Interestingly, it is of major relevance to note that among the clinical manifestations of systemic sclerosis, it includes pulmonary involvement in the form of a restrictive syndrome secondary to interstitial pneumopathy resembling COVID-19 interstitial pneumonia.

In our experience,[2] however, all cases of nucleolar pattern were subsequently tested for anti-Extractable Nuclear Antigens (anti-ENAs), as previously described,[3] and no one was positive for anti-topoisomerase I, whereas in Chang's study no anti-ENAs were tested for.

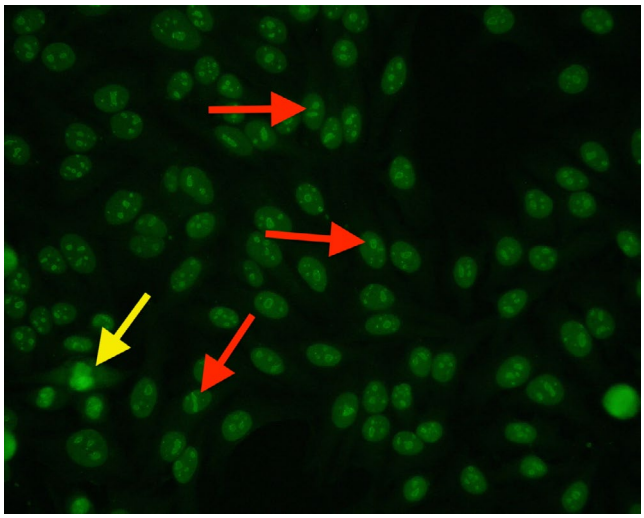

FIGURE 1 Substrate: Hep-2 cells, magnification ×40. Diffuse nucleoli positivity (red arrows), presence of perichromosomal fluorescence during the mitotic phase (yellow arrow)

The lack of positivity for the known anti-ENA reactivities clearly means that we are dealing with unknown target antigens that need to be identified in order to better understand the underlying pathophysiological mechanisms. It would be very interesting to verify and confirm the frequency of the nucleolar ANA pattern in this peculiar setting of patients by other multicenter studies with the aim then to characterize this reactivity and to identify the underlying molecular target

TABLE 1 ANA data and related information in patients with COVID-19 from different cohorts

Study population (M/F)	Age range	Hospital / country	ANA Positive rate	Prevalent ANA pattern	Patient type
12/8	42–85	Huangshi Central Hospital, Hubei, China	50%	Anti–SSA/Ro 60 kDa (25%)	Critical ill patients with COVID−19
21/8	43–85	Evangelismos Hospital, Athens, Greece	34.5%	Nucleolar ANA pattern (24%)	Severely ill patients with COVID−19 patients
17/16	22–90	IRCCS Azienda Ospedaliero-Universitaria Bologna, Italy	33.3%	Nucleolar (36%) and speckled (36%) ANA pattern	Consecutive patients with COVID−19
64 patients	27–89	Harborview Medical Centers in Seattle, Washington (USA)	25%	Anti-RNP (12.5%)	41% receiving care in the intensive care unit

Abbreviations: ANA, antinuclear antibody; COVID-19, coronavirus disease 2019.

because it could prove useful in understanding its significance and possible pathophysiological mechanisms.

Extending the evaluation of ANA in COVID-19 to other experiences, we can observe a similar prevalence to ours in a Greek study,[4] where the authors found an ANA positivity in 10 patients out of 29 (34%), and, interestingly, 7 of them exhibited a nucleolar ANA pattern. Moreover, two recent studies from Nanjing (China) and from Seattle (United States) reported a frequency of ANA of 50% and 25% respectively, even though the detection of these reactivities was not carried out by indirect immunofluorescence but by immunochemical method.[4,5]

Results of ANA detection and characterization in patients with COVID-19 from different reported cohorts are shown in Table 1.

We and others observed that ANA-positive patients had a worse prognosis compared with the negative ones with respect to COVID-19 disease, but there are a number of limitations that prevent conclusions from being drawn, ranging from the low number of patients studied, the different methods used for autoantibodies detection and the genetic heterogeneity of the patients included in the different studies.

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CONFLICT OF INTEREST

All authors declared no competing interests for this work.

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