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Review

Anti-NuMA1 and anti-NuMA2 (anti-HsEg5) antibodies: Clinical and immunological features: A propos of 40 new cases and review of the literature

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ABSTRACT

Objective: Anti-NuMA1 and anti-NuMA2 antibodies are antinuclear antibodies (ANA) targeting the mitotic spindle apparatus. Our objective was to determine their clinical and immunological features and to review the literature available data.
Patients and methods: Between 2004 and 2008, 36,498 sera were analyzed for the presence of ANA, which included anti-NuMA1 and anti-NuMA2 antibodies. Clinical and immunological features of patients with positive anti-NuMA1 and anti-NuMA2 antibodies (titer $\geq$1/320) were retrospectively collected and analyzed. A review of the literature was secondly performed.
Results: Out of the 36,498 sera analyzed, 10,585 sera were positive for ANA (29%). Out of ANA positive sera, 40 sera (0.38%) (40 different patients) were positive for anti-NuMA antibodies: 27 anti-NuMA1 (0.26%) and 13 anti-NuMA2 (0.12%). Compared to anti-NuMA2 positive patients, anti-NuMA1 positive patients were more often female (81.5% versus 46%; $P=0.03$), had more frequently a connective tissue disease (CTD) (40.7% versus 0%; $P=0.016$) and higher serum titers (877 ± 466 versus 443 ± 278; $P=0.007$). The anti-NuMA1 positive CTD were either Sjögren's syndrome (SS) (54.5%) or systemic lupus erythematosus (SLE) (45.5%). In the literature, 164 anti-NuMA positive patients (133 anti-NuMA1 and 31 anti-NuMA2) have been reported. Combining the reported cases to ours, up to 67.5% of anti-NuMA positive patients had an autoimmune disease, mostly pSS in 34% (31/90) and SLE in 31% (28/90). Anti-NuMA1 antibodies were the single positive ANA in 46% of anti-NuMA1 positive SS and 47% of anti-NuMA1 positive SLE, and anti-NuMA2 antibodies in 2/2 and 87.5%, respectively.
Conclusion: Detection of anti-NuMA1 and anti-NuMA2 antibodies is very uncommon. When present, they are mostly associated with connective tissue disease, mainly Sjögren syndrome and systemic lupus. Clinicians may be aware that in these latter conditions, anti-NuMA antibodies may be the single serological marker.

Contents

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1. Introduction

Anti-Nuclear Mitotic Apparatus (NuMA) antibodies 1 and 2 belong to the family of auto-antibodies against mitotic spindle apparatus (MSA), a subtype of antinuclear antibodies (ANA), which have been described for the first time in 1981 [1]. Anti-NuMA1 and anti-NuMA2 differ by their antigenic target, anti-NuMA1 targeting the NuMA and anti-NuMA2 the Kinesin Eg5 (HsEg5) [2]. NuMA and HsEg5 are the most common spindle antigens. NuMA is a 236 kDa nuclear matrix protein, which is distributed to the pericentrosomal region at each spindle pole during mitosis. NuMA has been shown to be involved for the terminal phases of chromosome separation and/or nuclear reassembly. HsEg5 is a 115 kDa protein member of the BimC family of kinesin-like proteins, distributed throughout the spindle during cell division [2–4]. These features lead to a different immunofluorescent pattern between anti-NuMA1 and anti-NuMA2, anti-NUMA1 being detected in the interphase and mitotic cells and anti-NuMA2 antibodies only in mitotic cells [3] (Fig. 1).

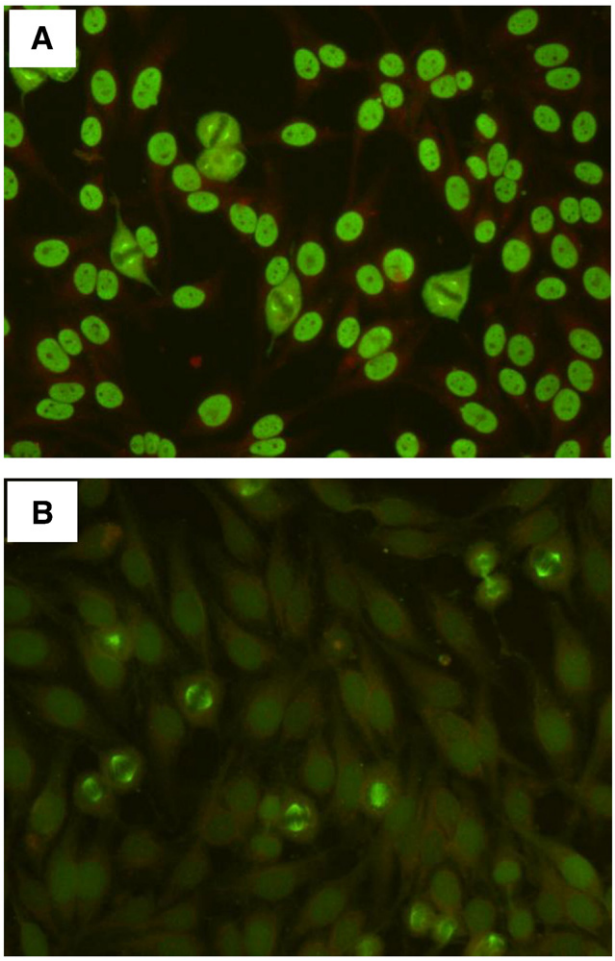

Fig. 1. Indirect immunofluorescent pattern of serum containing anti-NuMA1 antibodies (Fig. 1A) and anti-NuMA2 antibodies (Fig. 1B): A) Anti-NuMA1 antibodies are detected in interphase and at the mitotic spindle poles of metaphase and anaphase cells. B) Anti-NuMA2 (HsEg5) are detected only in the spindle poles of metaphase or anaphase cells.

Few studies have assessed the prevalence and clinical correlation of anti-NuMA1 and anti-NuMA2 antibodies. Their prevalence among sera tested for ANA is estimated to be less than 1% [5,6]. They are reported to be associated with several conditions, mainly connective tissue diseases [4–9], autoimmune liver disease [10] and infections [11].

In the present study, we assessed the prevalence and the clinical significance of anti-NuMA1 and 2 antibodies from a monocentre series of 40 patients, and secondly we reviewed the available data in the literature.

2. Patients and methods

2.1. Patients

Between 2004 and 2008, 36,498 sera were tested for antinuclear antibody (ANA), including anti-NuMA1 and anti-NuMA2 antibodies in the department of clinical immunochemistry of a university hospital. We retrospectively collected and analyzed clinical and immunological data of patients with positive anti-NuMA1 and anti-NuMA2 antibodies. A review of the literature was secondary performed to compare our results to those previously reported.

2.2. Immunological tests

Antinuclear Antibodies (ANA) were detected using an indirect immunofluorescence on HEp-2000 cells (Immuno Concepts, Sacremento, USA) with a cut-off of positivity upper than 1/80. Anti-NuMA1 and anti-NuMA2 antibodies were defined by their immuno-fluorescence aspect and were considered positive with a titer $\geq$320. Anti-Extractable Nuclear Antigen Antibodies, including anti-SSA (anti-Ro 52/60), anti-SSB (anti-La), anti-RNP, anti-Sm, anti-scl70, anti-JO1 and anti-PM1, were detected using a Multiplexed Microparticule-based Luminex immunoassay (AtheNA Multi-Lyte, Ingen, Antony, France). Anti-dsDNA antibodies were detected and quantified using enzyme-linked immunosorbent assay (ELISA) (Eti dsDNA, DiaSorin, Antony, France) and considered positive with a titer greater than 28 IU/mL.

2.3. Statistical analysis

Categorical variables were compared using Fisher's exact or chi-square tests, and continuous variables using the *t*-test or Mann *U* test when appropriate. A *P*-value$\leq$0.05 was considered statistically significant. All analyses were performed using the MedCalc® software version 10.0.1.0 (Mariakerke, Belgium).

2.4. Literature review

We reviewed the MEDLINE (National Library of Medicine, Bethesda, MD) database from 1950 to 2008, using and combining the following key-words: “NuMA”, “HsEg5”, “mitotic spindle apparatus”, “MSA”, “Connective Tissue Disease”, “systemic lupus erythematosus (SLE)”, “Sjögren syndrome (SS)”, “thyroiditis” and “autoimmune disease”. Available articles were secondary analyzed and only articles with a focus on the prevalence and the clinical significance of anti-NuMA1 and anti-NuMA2 antibodies were retained.