Editorial paper

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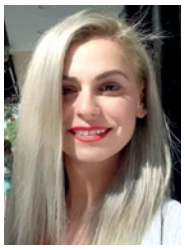
On the role of anti-cN1A antibodies in sporadic inclusion body myositis and beyond: a challenging task full of surprises



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Autoantibodies recognising cytosolic 5′-nucleotidase 1A (cN1A) were originally described as specific markers of sporadic inclusion body myositis (sIBM) [1]. Sporadic inclusion body myositis is an immune-mediated idiopathic inflammatory myopathy (IIM) most commonly noted in men over the age of 50 [1]. The diagnostic significance of autoantibodies in sIBM has been questioned and myositis-specific (MSA) or myositis-associated autoantibodies (MAA), which are frequently noted in other IIMs such as dermatomyositis (DM), polymyositis (PM), or anti-synthetase syndrome (ASS), are not common in this form of myositis. The treatment of these diseases is at times puzzling and drug-induced remission is not favourable [2].

The pathogenic role of anti-cN1A in sIBM remains elusive, though lately attempts have been made to assess its impending pathogenicity [1]. How myopathy is also initiated in autoimmune rheumatic diseases and whether common pathophysiologic mechanisms do really exist are not yet clear [3–6]. Very recently, Yamashita et al. [7] injected wild-type C57BL6 mice with three of the immunodominant cN1A peptides. The injected mice developed autoantibodies against cN1A and a subgroup of them lost weight and showed decreased motor activity. Infiltrating CD8-positive T cells into myofibres and abnormal protein aggregates were also noted [7]. Such results raise the possibility that an antigen-driven loss of immunological tolerance to cN1A may indeed play a role in the induction of sIBM. Those experiments must accelerate research on the enigmatic role of cN1A in sIBM. However, the resemblance of the cN1A-induced, immunization-perpetrated damage inadequately resembles the human disease and the murine model is far from being considered perfect.

In routine practice, clinicians would like to know whether anti-cN1A antibody is a sensitive and specific marker of sIBM, as this could drive the differential diagnosis. The original enthusiasm based on reports suggesting that cN1A is an autoantibody with very high specificity for sIBM has been dampened by subsequent reports raising concerns due to its imperfect specificity. Issues related to false positivity or negativity, and the questionable significance of borderline tests, are also clinically relevant as they may confuse the treating physician.

In this research area, considerable recent efforts have focused on measuring autoantibodies in large multicentre cohorts of patients. Worth noting is that the availability of commercial diagnostic anti-cN1A antibody assays has accelerated research, although the standardization of these tests is still lacking. It is also troubling that ANA detected by indirect immunofluorescence (IIF) in sIBM sera clearly do not demonstrate a consistent IIF pattern associated with anti-cN1A reactivity. Various antigen-specific assays detecting this autoantibody have been developed and commercialized, including enzyme-linked immunosorbent assays (ELISAs), line immunoassays (LIAs) and addressable laser bead immunoassay (ALBIA). What emerges from such studies is extremely helpful but not immediately desirable.

Concerning the specificity of the autoantibody, it has become apparent that anti-cN1A is not as specific for sIBM as was originally assumed. Early studies estimated

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the specificity of anti-cN1A for sIBM in the range 87–100%, which was rather remarkable and intriguing. However, more recent studies have produced less impressive data. In a cohort of our centre including 260 sera from patients without definite sIBM or any other evidence of IIM which have been tested by an LIA for MSA and MAA (Euroimmun, Lübeck, Germany), 17/260 (6.5%) serum samples were found positive for anti-cN1A (overall specificity 93.5%). One proved to be a patient with anti-synthetase syndrome and one with dermatomyositis, while 11 more had other autoimmune rheumatic diseases (5 had systemic lupus erythematosus [SLE], 3 had systemic sclerosis [SSc], 2 had rheumatoid arthritis, and 1 had anti-MPO+ ANCA+ vasculitis). The remaining 4 did not have any rheumatic disease; one had psoriasis and autoimmune thyroiditis, one had muscle weakness of unidentified cause, while two were healthy individuals (one of whom had detectable anti-Ro52 antibodies). A recent multicentre Italian study comprehensively corroborated such findings [8]. Amongst the 340 samples, 20 (5.9%) tested positive for anti-cN1A; 75% of those were female [8]. Out of those 20, only 2 (10%) were definitely diagnosed with IBM; 6 had other IIMs, 6 had seronegative arthritis, 2 had undifferentiated connective tissue disease, 1 had myasthenia gravis, 1 had interstitial lung disease, 1 was diagnosed with metastatic pancreas carcinoma, and in 1 no definite diagnosis was reached.

Another recent study tested 567 individuals including 182 patients with IIM [9]. None of the 100 blood donors or the 121 systemic sclerosis patients had detectable anti-cN1A antibodies. However, 10% of the 164 SLE tested positive. Also, 15.2% of the non-IBM IIM patients were seropositive [9]. Amlani et al. [10] found that 5.1% of 78 healthy individuals had anti-cN1A antibodies as detected by an ALBIA using a full-length human recombinant protein. A Japanese study also found that 6% of patients with SLE, 8% with SSc, and 4% with pSS had anti-cN1A antibodies [11]. In another European study, anti-cN1A autoantibodies were found on average in 12% of pSS patients and 10% with SLE from 5 European centres [12]. In their meta-analysis, Mavroudis et al. [13] failed to demonstrate any significant usefulness of anti-CN1A antibodies in the diagnosis of sIBM.

Another clinically relevant question is whether anti-cN1A antibodies are prognostic markers of disease activity or response to treatment. The results are heterogeneous and conflicting. Diederichsen et al. [9] found that dysphagia was more frequent in anti-cN1A positive vs. negative sIBM patients, and this has also been confirmed more recently [14]. In their univariable analysis, Amlani et al. [10] reported that sIBM patients with more severe muscle weakness were more likely to be anti-cN1A positive. Other published data do not correlate anti-cN1A antibodies with particular clinical, electromyographic, or histopathological features in sIBM [15].

In conclusion, anti-cN1A immunoreactivity is more frequent in sIBM and may play a role in the pathogenesis of the disease. Its isolated autoantibody testing for diagnostic purposes must be treated with caution, taking into account its rather inadequate specificity. Profiling assays based on MSA or MAA tend to provide a more reliable picture. Nevertheless, intense research assessing the role of anti-cN1A in sporadic inclusion body myositis is urgently warranted.

The authors declare no conflict of interest.

References

1. Greenberg SA. Inclusion body myositis: clinical features and pathogenesis. Nat Rev Rheumatol 2019; 15: 257–272, DOI: 10.1038/s41584-019-0186-x.
2. Grazzini S, Rizzo C, Conticini E, et al. The role of bDMARDs in idiopathic inflammatory myopathies: A systematic literature review. Autoimmun Rev 2023; 22: 103264, DOI: 10.1016/j.autrev.2022.103264.
3. Mogyoróssy S, Nagy-Vincze M, Griger Z, et al. Novel aspects of muscle involvement in immune-mediated inflammatory arthropathies and connective tissue diseases. Autoimmun Rev 2023; 22: 103311, DOI: 10.1016/j.autrev.2023.103311.
4. Syrmou V, Liaskos C, Ntavari N, et al. COVID-19 vaccine-associated myositis: a comprehensive review of the literature driven by a case report. Immunol Res 2023; 71: 537–546, DOI: 10.1007/s12026-023-09368-2.
5. Pagkopoulou E, Simopoulou T, Maragkouli E, et al. Arthritis and myositis in a patient treated with programmed cell death-1 (PD-1) inhibitor pembrolizumab for lung cancer. Mediterr J Rheumatol 2020; 31: 355–357, DOI: 10.31138/mjr.31.3.355.
6. Gasparotto M, Franco C, Zanatta E, et al. The interferon in idiopathic inflammatory myopathies: Different signatures and new therapeutic perspectives. A literature review. Autoimmun Rev 2023; 22:103334, DOI: 10.1016/j.autrev.2023.103334.
7. Yamashita S, Tawara N, Zhang Z, et al. Pathogenic role of anti-cN1A autoantibodies in sporadic inclusion body myositis. J Neurol Neurosurg Psychiatry 2023; 94: 1018–1024, DOI: 10.1136/jnnp-2023-331474.
8. Porcelli B, d'Alessandro M, Gupta L, et al. Anti-cytosolic 5'-nucleotidase 1A in the diagnosis of patients with suspected idiopathic inflammatory myopathies: An Italian Real-Life, Single-Centre Retrospective Study. Biomedicines 2023; 11: 1963, DOI: 10.3390/biomedicines11071963.
9. Diederichsen LP, Iversen LV, Nielsen CT, et al. Myositis-related autoantibody profile and clinical characteristics stratified by anti-cytosolic 5'-nucleotidase 1A status in connective tissue diseases. Muscle Nerve 2023; 68: 73–80, DOI: 10.1002/mus.27841.

10. Amlani A, Choi MY, Tarnopolsky M, et al. Anti-NT5c1A autoantibodies as biomarkers in inclusion body myositis. Front Immunol 2019; 10: 745, DOI: 10.3389/fimmu.2019.00745.
11. Muro Y, Nakanishi H, Katsuno M, et al. Prevalence of anti-NT5C1A antibodies in Japanese patients with autoimmune rheumatic diseases in comparison with other patient cohorts. Clin Chim Acta 2017; 472: 1–4, DOI:10.1016/j.cca.2017.07.002.
12. Rietveld A, van den Hoogen LL, Bizzaro N, et al. Autoantibodies to cytosolic 5'-nucleotidase 1A in primary Sjögren's syndrome and systemic lupus erythematosus. Front Immunol 2018; 9: 1200, DOI: 10.3389/fimmu.2018.0120013.
13. Mavroudis I, Knights M, Petridis F, et al. Diagnostic accuracy of anti-CN1A on the diagnosis of inclusion body myositis. A Hierarchical Bivariate and Bayesian Meta-analysis. J Clin Neuromuscul Dis 2021; 23: 31–38, DOI: 10.1097/CND.0000000000000353.
14. Lucchini M, Maggi L, Pegoraro E, et al. Anti-cN1A antibodies are associated with more severe dysphagia in sporadic inclusion body myositis. Cells 2021; 10: 1146, DOI: 10.3390/cells10051146.
15. Paul P, Liewluck T, Ernste FC, et al. Anti-cN1A antibodies do not correlate with specific clinical, electromyographic, or pathological findings in sporadic inclusion body myositis. Muscle Nerve 2021; 63: 490-496, DOI: 10.1002/mus.27157.