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ICI-related Myositis/Myasthenia gravis: an overlap or not?

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BACKGROUND

It's still debated if Immune checkpoint inhibitors (ICI)-related myositis/myasthenia gravis (MG) represents a distinctive overlap syndrome or a myositis with MG-like presentation.
These patients can present acetylcholine receptor (AchR) antibodies, but their pathogenicity is debated. Herein we describe a unique case of ICI-related myositis/MG with a dual positivity for both Ach-R and MUSK antibodies (abs), in which functional studies on the AChR abs were also performed.

METHODS

Serum was firstly tested for AchR and MUSK antibodies by radioimmunoassay (RIA) and then confirmed with live-cell based assay (L-CBA).
Antibody-mediated complement activation against AchR was assessed using Fluorescence-Activated Cell Sorting (FACS) (for further methodological details see Figure 1).
Repetitive Nerve stimulations (RNS) was performed on a distal, proximal and cranial motor nerve in all the patients. Stimulated single fibre electromyography (SFEMG) of the frontalis was also performed.

RESULTS

A 77-year-old man diagnosed with small cell lung cancer (SCLC) developed myalgia, head drop, dyspnea, and asthenia after the second administration of carboplatin and atezolizumab.
Blood tests revealed elevated creatine phosphokinase levels (3826 U/L), leading to suspicion of ICI-related myositis, which was confirmed by both EMG and muscle MRI.
Despite the absence of fatigability, the patient showed a positivity for anti-AChR abs (2.1 nmol/L in RIA, normal values <0.5) e anti-MuSK abs (0.06 nmol/L in RIA, normal values <0.05). These results were confirmed by L-CBA.
No complement activation against AChR was detected by FACS but differently from sera of one patient with sporadic MG (Figure 1).
RNS and SFEMG were also negative.

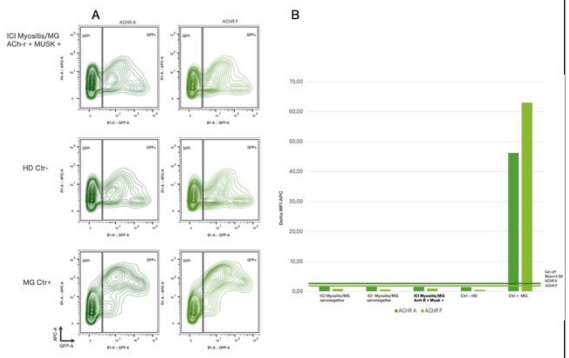

Figure 1 Analysis of complement activation (C3/C3b/iC3b detection) by patient sera against clustered adult (A) and fetal (F) AChR using FACS.
A. Contour plots from sera of the patient, a healthy donor and a MG patient included as positive control.
B. Histogram comparing delta MFI of APC obtained from testing sera from ICI related myositis/MG and the values obtained from the healthy donor (HD) and MG.
All MG-Myositis ICI-related sera, including the one positive for anti-AChR antibodies, have a value below the experimental cut off.

Methods: sera were tested for reactivity against clustered adult (A) and fetal (F) anti-AChR antibodies using L-CBA, then were assessed for antibody-mediated complement activation against AChR using FACS. Complement activation was induced by incubating HEK293 cells transfected for clustered A- or F-AChR with heat inactivated patient sera (dilution 1:20) and normal human serum (NHS) as source of complement components. Cells were then fixed in 2% paraformaldehyde and subsequently stained with a mouse anti-human C3/C3b/iC3b antibody, followed by an APC-tagged rat anti-mouse secondary antibody. Complementdeposition was quantified as delta mean fluorescence intensity (MFI) of APC between GFP-positive (transfected) and GFP-negative cells.
The positivity cut-off was established as the mean plus five standard deviations of the delta-MFI of APC obtained from healthy control samples.

CONCLUSIONS

The positivity for both AChr and MUSK antibodies, together with absence of fatiguability, the lack of complement activation against AChR and the negativity of neurophysiological tests, might support the hypothesis that these antibodies are not pathogenetic but just an epiphenomenon. MG-like symptoms may be the result of a peculiar pattern distribution of muscle inflammation in ICI-related myositis, in absence of a real disruption of neuromuscular junction. Prospective, large studies are needed to confirm this hypothesis, but a definitive understanding of pathogenesis is essential to guide a more targeted and effective therapeutic approach.

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