ERAD, 2022, Volume 1, Issue 1, pages 1-3

Commentary

Autoantibodies as prognosticators of treatment outcome in cancerous diseases: learning from immune-check point inhibitors

Running title: ANA, immune-check inhibitors and cancer

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Abstract

The diagnostic and clinical significance of autoantibodies, and in particular anti-nuclear antibodies in predicting response to treatment of cancerous patients under immune checkpoint inhibitors (ICIs) is a topic of intense research. While some studies reported that the presence of ANA or the levels of autoantibodies does not predict response to treatment, others have found a favorable course in patients with preexisting autoantibodies. Conflicting are also the results reporting on the likely association between the pre-existence or the development of the autoantibodies over the course of ICIs initiation and the appearance of immune-related adverse events. We discuss those data in great detail, and we comment on a recent study, as well as our own experience, on the presumed associations between autoantibody positivity and treatment outcome. We also address the role of anti-Ro52 antibodies, an autoantibody marker which may need meticulous assessment in patients with malignant disorders, as a potential prognosticator of disease-progression and response to treatment.

(Submitted 12 March 2022; revised 11 April 2022; accepted 19 April 2022)

Keywords- Antinuclear antibodies; autoantibody; immune-check point inhibitor; immune-related adverse events; non-small cell lung cancer; ovarian cancer

I. INTRODUCTION

We would like to raise our appreciation of a recent study by Barth et al. (1) and comment on their findings, which are of great interest. These investigators assessed the clinical significance of pre-existing anti-nuclear antibodies (ANA), i.e. autoantibody positivity at baseline, in predicting the outcome of treatment response and the development of immune-related adverse events (irAEs) following treatment with immune checkpoint inhibitors (ICIs) (1). These authors have studied various autoantibodies including ANA, ENA (extractable nuclear antigen), inflammatory myositis, autoimmune liver disease related autoantibodies and RF (rheumatoid factor) /anti-CCP (cyclic citrullinated peptide) and their presence in sera of patients with cancer was associated with ICIs treatment response, as well as irAEs (1).

The study by Barth et al. (1) is not the first to be conducted on this topic (2-7). The prognostic value of autoantibodies, mainly those against nuclear antigens, has been assessed in the past, and the published data are conflicting. A recent systematic review assessed the prevalence of autoantibodies in patients with organ-specific ICIs-associated irAEs and determined their significance as potential pretreatment biomarkers (8). In a single centre Japanese study, Mouri et al. (4) assessed the association between ICIs and ANA presence in a large number (n=266)

of patients with non-small cell lung cancer (NSCLC), who received anti-PD-1/PD-L1 antibody monotherapy (single-agent nivolumab, pembrolizumab, and atezolizumab). The authors conclusions were that ANA presence, or the levels of autoantibodies could neither predict response to treatment nor the induction of irAEs. In contrast, a prognostic significance was found for autoantibody presence in an Italian retrospective study that included 92 patients with metastatic non-small cell lung cancer (mNSCLC) and assessed the prognostic value of multiple autoantibody specificities emerging within the first 30 days of Nivolumab treatment (2). These investigators found that the early appearance of more than 1 autoantibody specificity, including ANA, extractable nuclear antigens (ENAs) and anti-smooth cell antigens (ASMAs) correlated with prolonged progression-free survival (PFS) and overall survival (OS) and with the risk for the development of irAEs leading the authors to conclude that the increased serum levels of ANA, ENA and/or ASMA, which are induced by Nivolumab administration are predictive markers of a positive outcome in patients with mNSCLC (2).

Another large retrospective study analyzing 137 patients with NSCLC concluded that cancerous patients with autoantibody (ANA, rheumatoid factor, antithyroglobulin and antithyroid peroxidase antibodies) at baseline, who were treated with ICIs had a better outcome (as defined by PFS) in comparison to patients with autoantibody negativity (3). Of interest, patients with established autoantibodies appeared to have significantly higher response rate to ICIs. However, ANA as well as rheumatoid factor and/or antithyroid antibodies were not *per se* associated with ORR and DCR (3).

In contrast to the above, other smaller studies like those by Morimoto et al. (5) including 77 patients and Yoneshima et al. (6) including 83 patients with advanced NSCLC, respectively, have been able to report significantly shorter PFS and OS in patients with ANA positivity. The inconsistent results amongst studies may be due to the distinct design of the study, the cut off used for autoantibody determination, the different methods used for autoantibody detection and the diverse cohorts of patients, which have been analyzed.

In the recent study by Barth et al.(1) amongst the 44 patients assessed, most had non-small lung cancer (n=15), renal cell carcinoma (n=11) head and neck cancer (n=7) and bladder cancer (n=6); other cancers were also tested in small numbers. The authors found no association between the presence of ANA (tested by indirect immunofluorescence at a cut off of 1/80) and the outcome of response to treatment with the examined clinical endpoints i.e. disease control rate, objective response rate and progression-free survival. No association was also found with any other autoantibody positivity leading the authors to conclude that the presence of autoantibodies cannot predict treatment response. Two further points were made by the investigators. The increase of ANA levels during ICIs treatment did not add predictive value to treatment outcome, and no evidence of an association between irAEs and autoantibody positivity was also present. Furthermore, ANA levels at both timepoints and the increase in ANA titers were no significant predictors of treatment outcomes. Subgroup analysis stratified by tumor entity did not reveal significant differences in response rates (DCR and ORR) except for DCR in patients with NSCLC after 8–12 weeks of ICIs treatment. Finally, they did not observe evidence of an association between elevated autoantibody- or ANA titers with the occurrence of grade 3 or higher irAEs.

ANAs are probably the most frequent autoantibodies found in ICIs-treated patients with cancerous disease, irrespectively of the type of cancer. Several investigators have considered this an epiphenomenon, as ANA are frequently found in patients with cancer, as well as healthy individuals, especially those of older age. We have been able to assess this in a greater detail. Our study was not particularly focused on the effect of ICIs in ANA development or their association with treatment response rates or the development of irAEs but rather in the presence of autoantibodies in patients with cancer. We tested serum samples from 490 patients, including 102 patients with lung cancer, but also 130 patients with ovarian cancer, 135 patients with colorectal cancer, 59 with breast cancer, 19 patients with pancreatic cancer, 15 patients with urinary bladder cancer, and 30 patients with head and neck cancer. Our study, probably the largest of its kind so far, addressed the antigen specificity of ANA, and in particular that against anti-Ro52 antibodies. We selected this autoantibody on the basis of preliminary data, which were also externally validated (9), showing that this autoantibody is probably one of the most prevalent in cancerous diseases, at least in some types of those (10). We have found that Ro52 autoantibodies were significantly more frequent in patients with ovarian cancer (30%) than in patients with other cancerous disease, a peculiar finding which we could address its immunopathophysiological relevance (10). We also found that those patients with ovarian cancer and anti-Ro52 antibodies had significantly better overall survival compared to those who lacking those autoantibodies (10). When we assessed the epitope specificity of anti-Ro52

antibodies, we were able to provide data suggesting that patients with ovarian cancer have an anti-Ro52 antibody epitope specificity which is distinct to that noted in typical anti-Ro52 positive diseases such as those of systemic lupus erythematosus and Sjogren's syndrome (10).

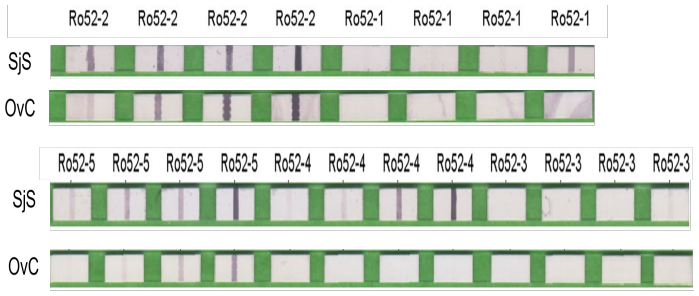

***Fig. 1**. Representative anti-Ro52 epitope specificity against five Ro52 polypeptides (Ro52-1 to 5, in four different dilutions of two sera, one from a patient with ovarian cancer (OvC) compared to a patient with Sjogren syndrome (SjS) which shows different epitope specificity for Ro-52 polypeptide 4. That peptide is recognized by the SjS serum but not the OvC serum.*

II. CONCLUSION

In conclusion, the clinical significance of preexisting autoantibody status, and in particular of anti-nuclear antibodies, in relation to treatment outcome, such as that related to treatment with ICIs or its association with the development of irAEs following treatment, such as that of ICIs, remains an unresolved issue.

AUTHOR CONTRIBUTIONS

VP and DPB drafted the manuscript. EP, CL and CT revised the manuscript. The figure was prepared by CL. All authors approved the final version of the manuscript.

CONFLICT OF INTEREST

All Authors declare no conflict of interest.

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