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Patients with checkpoint inhibitor-induced inflammatory arthritis do not become seropositive for anti-cyclic citrullinated peptide when followed over time

Immune checkpoint inhibitors (ICIs) have enhanced the treatment of many advanced and metastatic cancers (1). Rheumatologists are increasingly encountering immune-related adverse events (irAEs) caused by ICI treatment, most commonly inflammatory arthritis (IA) (2). The majority of patients with ICI-induced IA, more than 90% in one systematic review (3), are seronegative for classic rheumatoid arthritis (RA)–associated autoantibodies (ie, anti-cyclic citrullinated peptide [anti-CCP] antibodies) at the time of arthritis presentation. Given that ICI-induced IA is a potential model for early IA, how the autoantibody response evolves over time is of significant interest. A considerable proportion of patients with ICI-induced IA will have persistent symptoms even after ICI cessation (4). It is unknown whether patients with persistent IA symptoms after ICI therapy remain seronegative or whether they seroconvert over time. We aimed to determine whether patients observed serially for ICI-induced IA would develop anti-CCP antibodies.

Patients were participants in a longitudinal observational study of rheumatic irAEs (approved by Johns Hopkins Institutional Review Board, IRB00123172). Clinical data, including cancer history and treatment, clinically obtained laboratory studies, and disease activity measures, were collected as part of this ongoing study. Thirty-four patients with a baseline blood sample (defined as the first presentation to the rheumatology clinic) and at least one follow-up blood sample were tested for anti-CCP antibodies (QUANTA Lite cyclic citrullinated peptide 3 immunoglobulin G enzyme-linked immunoassay [ELISA]; Inova). Eighteen patients had two blood samples taken at visits after their initial presentation to rheumatology, six patients had three subsequent blood samples after initial presentation, and one patient had four subsequent samples. All available longitudinal samples were tested for included patients.

Of the 34 patients, 16 were women (47%), and the average age was 59 (SD 15.5). Nineteen patients (56%) had other irAEs in addition to IA. Patients were treated with ipilimumab/nivolumab combination, ipilimumab, nivolumab, pembrolizumab, or durvalumab. The most common tumor types were melanoma (n = 17), non–small cell lung cancer (n = 4), and cutaneous squamous cell carcinoma (n = 2). Patients had an average Clinical Disease Activity Index score of 18.4 (SD 11.9) at first visit to rheumatology; eight (25%) had enthesitis, and four (12.5%) had tenosynovitis as part of their IA phenotype. Eight (25%) patients met American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2010 RA classification criteria. Twenty-eight (87.5%) required corticosteroids, 15 (46.9%) required conventional synthetic disease-modifying antirheumatic drugs, and 12 (37.5%) required biologics for treatment. Mean time from presentation to first follow-up sample was 4.8 months (SD 5.5). The longest time from presentation to any follow-up sample was 24 months. Thirty-three of thirty-four patients were negative for anti-CCP antibodies at baseline (97%). Of those 33 patients, 1 was positive for anti-CCP antibodies on the second and third follow-up samples. The patient who was positive for anti-CCP antibodies at baseline was positive on the first follow-up sample and negative on the second. The two patients to test positive for anti-CCP antibodies were both treated with pembrolizumab but had different tumor types (pancreatic cancer and squamous cell carcinoma) and were different sexes, and one has survived long-term whereas the other is deceased. The remaining 32 patients were negative for anti-CCP antibodies in

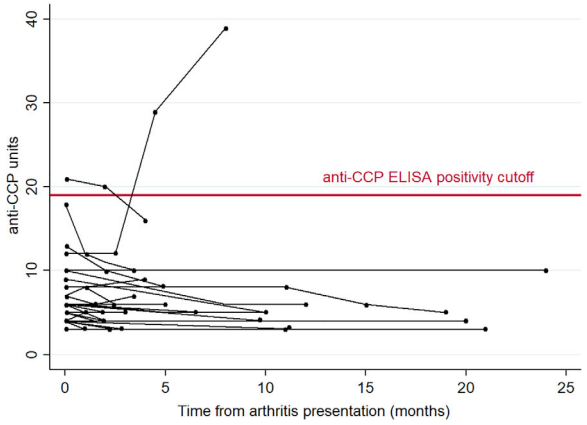

FIGURE 1. Anti-cyclic citrullinated peptide (anti-CCP) antibody levels over time for all included patients. ELISA, enzyme-linked immunoassay.

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all subsequent samples (94% of total). Figure 1 depicts anti-CCP antibody levels at each point in time measured for the included participants, with the threshold for positivity of the anti-CCP ELISA noted.

In this study of patients observed clinically for ICI-induced IA, the vast majority remained seronegative for anti-CCP antibodies on serial evaluation. Patients were observed for up to 2 years after their initial rheumatology appointment because of continuing symptoms of arthritis but did not seroconvert. This suggests a key difference in pathogenesis between ICI-induced IA and RA and may represent a limitation in using patients with ICI-induced IA as a model for early seropositive RA. Similarities may be stronger to peripheral spondyloarthritis or other forms of seronegative IA, such as seronegative RA. The observation that patients remain seronegative may have implications for treatment because therapies such as rituximab that often favored in the context of malignancy are less effective in the seronegative IA population (5,6).

The study is limited by the number of patients and the short duration of follow-up in some participants, which was primarily due to death from their underlying malignancies. Nine of the patients in this study (28%) had died at the time of data analysis. Future multicenter studies should further evaluate autoantibody status over time in larger groups of patients, focusing on both known and yet to be discovered autoantibodies.

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All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Cappelli had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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