Rheumatic manifestations among cancer patients treated with immune checkpoint inhibitors

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Abstract

Background: The use of immune checkpoint inhibitors (ICI) has grown incessantly since they were first approved in 2014. These monoclonal antibodies inhibit T cell activation, yielding a dramatic tumor response with improved survival. However, immunotherapy is frequently hampered by immune adverse events (iAE) such as hypophysitis, colitis, hepatitis, pneumonitis and rash. Until recently, rheumatic side effects were only infrequently reported.

Aim: To describe the rheumatic manifestations encountered among patients treated with ICIs in a large tertiary cancer center in Israel.

Methods: The cancer center’s patient registry was screened for patients who had ever been treated with ipilimumab, pembrolizumab and/or nivolumab with relevant data gathered from clinical charts.

Results: Rheumatic manifestations were encountered in 14 of 400 patients (3.5%) who had received immunotherapy between January 1st 2013 and April 30th, 2017. The most common rheumatic manifestation was inflammatory arthritis (85%) for which a third (4/11) had a clear cut predisposing factor such as a personal or family history of psoriasis, a prior episode of uveitis or ACPA positivity. Pulmonary sarcoidosis and biopsy-proven eosinophilic fasciitis were diagnosed in two additional patients. Treatment with NSAIDS was mostly unsuccessful while steroid therapy was beneficial in doses ≥20 mg/d. Methotrexate enabled steroid tapering without an excess of side effects or tumor progression in the short follow-up available. Overall, rheumatic manifestations tended to occur later in the course of immunotherapy as compared to other iAE.

Conclusions: Our findings underscore that rheumatic iAE are part of the side effect profile of ICIs and require heightened awareness as these therapies are becoming the standard of care for various malignancies. We show that these appear later in the course of iAEs and respond preferentially to high dose steroids. MTX appears effective as a steroid sparing agent.

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Carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1) [13,14], are under development. Immunotherapy is frequently hampered by immune related adverse events (iAEs), which occur due to immune stimulation or interference with tolerance. These events necessitate in some cases temporary or permanent discontinuation of treatment, corticosteroid therapy or other forms of immune-suppressive modalities. The most common iAE encountered in clinical trials include hypophysitis, colitis, hepatitis, pneumonitis and rash [15]. Frequency of grade 3–4 iAEs span from 10 to 15% for PD-1 blocking antibodies, 25–30% for CTLA-4 blocking antibodies and 55% for combination of PD-1 and CTLA-4 [10]. In most cases the toxicity is reversible.

Severe musculoskeletal side effects were infrequently reported in clinical trials. Over the past two years, sporadic cases reports, and more recently, two case series of rheumatic iAEs have been published [16,17], establishing this as a not-uncommon entity to which oncologists and rheumatologists should be aware. Moreover, delineation of the underlying mechanisms of anti-PD-1 mediated rheumatic iAEs may provide important insights on the involvement of this axis in autoimmune diseases. Indeed, the PD-1 axis is involved in maintaining peripheral tissue tolerance, and its dysregulation has been implicated in multiple models of autoimmune diseases, including systemic lupus erythematosus and rheumatoid arthritis [18]. Interestingly, PD-1 is increased on synovial lymphocytes of rheumatoid arthritis patients by extracellular vesicles [19], which are known to play important role in many types of autoimmune diseases [20]. Following these insights, it was recently suggested that development of PD-1 agonists may prove to be effective in autoimmune diseases such as rheumatoid arthritis [21].

Here we describe our series of patients with rheumatic iAEs, discuss the differences in the onset and course of these iAEs as opposed to the more typical iAEs. In addition, we propose a preliminary diagnostic work-up which shall facilitate earlier diagnosis and institution of appropriate therapy.

2. Methods

2.1. Patient population

We identified 400 advanced melanoma patients treated with ipilimumab, nivolumab, pembrolizumab or ipilimumab + nivolumab at the Sheba Medical Center between January 1st 2013 and April 30th, 2017. The medical records of patients were reviewed and rheumatic iAEs related to ICI therapy were identified in 14 patients. Severity was graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Response to treatment was defined by advanced imaging in multi-disciplinary meetings.

Twelve of the 14 patients were evaluated by a rheumatologist. Nine of the 12 were classified as having inflammatory arthritis (IA) based on history, physical examination, imaging and laboratory findings. Two additional patients had biopsy proven sarcoidosis and eosinophilic fascitis. Two patients with IA who were included in the series were not available for further rheumatologic evaluation. Demographic data, other iAE manifestations, treatment and response as well as articular and imaging findings were recorded by the treating oncologist and evaluating rheumatologist.

2.2. Ethics

Retrospective review of medical records was approved by the Institutional Review Board.

2.3. Statistics

Kaplan–Meier method was used to summarize the overall survival and progression free survival estimates from initiation of treatment. Kruskal–Wallis test and unpaired t-test with Welch’s correction were used to analyze differential onset of iAEs. P < .05 was considered significant.

3. Results

A total of 400 patients had received immunotherapy at our center, with one or a combination of ICIs. Rheumatic manifestations were encountered in 14 patients (3.5%). Twelve patients had melanoma, one an endometrial carcinoma and another, an undifferentiated sinusonal carcinoma. The average age of the patients was 61 ± 11 years and 57% were female (Table 1). Twelve patients had been treated with anti PD-1, one with combination therapy with anti CTLA-4 and anti PD-1 (ipilimumab and nivolumab) and a single patient had received only anti CTLA-4 (Table 1). Three patients had stable disease, 6 had partial response and 4 achieved complete remission (Table 1). One patient was treated with adjuvant ipilimumab after surgical resection of metastasis. Excluding one patient who has been lost to follow up, only one patient died, thus the median overall median survival was not reached over a median follow up of 27 (range 4–41) months. The median progression free survival was 24 (range 4–41) months (Table 1 and Fig. 1A–B).

A non-rheumatic iAE was noted in 8 (57%) of the patients, and in 7 of them, two or more body systems were involved (Table 1). The onset of non-rheumatic iAE was significantly earlier than the onset of the rheumatic iAE, occurring on average at 5.5 ± 1.2 m (range 1–22) m and 11.2 m ± 2.3 m (range 1–24) after initiation of immunotherapy (Fig. 1C). Detailed depiction of all non-rheumatic iAEs shows that only hepatitis occurred at late stage similar to rheumatic iAEs (Fig. 1D). Rheumatic iAE included the development of de-novo rheumatoid arthritis (RA), in an ACRA-positive patient, the development of seronegative oligoarthritis in a patient with a family history of psoriasis, new-onset fascitis, myositis and more. Treatment with NSAIDS was unsuccessful in the majority of patients while steroid therapy was beneficial in doses ≥20 mg/d. The addition of methotrexate (MTX) allowed steroid tapering where needed without an excess of side effects. Tumor necrosis factor inhibitors, which are used by oncologists to overcome ICI induced iAE such as severe colitis, were not used (Table 2).

4. Discussion

ICIs are playing an increasingly important role in the treatment of many types of solid and hematologic malignancies, particularly anti-PD-1. As ICI anti-tumor response is based on blocking negative regulators of immunity, iAEs are an inherent part of this therapy. Over the past couple of years, oncologists have become more familiar with iAEs, which are distinct from chemotherapy induced side effects. That being, rheumatic iAE have been scarcely reviewed until recently, the familiarity of the oncologist and rheumatologist with their presence and prevalence is low, while their optimal therapy and outcome have yet to be established. The present cases series is the third to be published since the beginning of 2017, highlighting the growing popularity of anti-PD-1 and the increasing awareness to the rheumatic iAEs associated with their use.

The average time to onset of a rheumatic iAE in our series was 11.2 months with only one patient developing polyarthritis as early as 1 month following initiation of anti PD-1 therapy (patient 14). The patient presented with diffuse arthralgia upon completion of cisplatinum based chemotherapy due to undifferentiated sinus-nasal carcinoma. A musculoskeletal exam failed to disclose clinical arthritis, perhaps due to the fact that he was receiving corticosteroids as part of the chemotherapy regimen at the time. Anti citrullinated cyclic peptide levels (ACPA), however, were extremely high (5-fold the upper level of normal). Four months following this initial rheumatologic evaluation, therapy with pembrolizumab was initiated due to the appearance of lung metastases on PET-CT. One month following this first course of immunotherapy, inflammatory polyarthritis involving small and large joints in a symmetrical pattern typical of RA, developed. Prednisone 60 mg/d was needed in order to achieve control of symptoms, which recurered upon tapering yet responded partially to the addition of MTX.