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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.

1. Introduction

Breakthrough in cancer immunotherapy has been achieved by blocking immune checkpoints, such as cytotoxic T-lymphocyte antigen 4 (CTLA-4) or programmed cell death 1 (PD-1). CTLA-4 mainly suppresses immune priming [1] while PD-1 modulates T cell receptor signaling [2], predominantly by interacting with PD-L1 (CD274) or PD-L2 (CD273) [3]. Ipilimumab, a fully human monoclonal antibody that blocks CTLA-4, was approved for the treatment of metastatic melanoma, after demonstrating superior overall survival in two randomized Phase III trials [4,5], as well as overall survival in the adjuvant setting [6]. An opposite effect is attained by using CTLA4-Ig (abatacept), which targets the co-stimulating molecules CD80/CD86, and is widely used in rheumatoid arthritis [7]. Antibodies blocking the PD-1 axis release the tonic inhibition off tumor-specific T cells to induce durable anti-tumor responses in a wide spectrum of tumor histologies [8,9]. Two anti-PD1 antibodies (pembrolizumab and nivolumab) and three anti-PD-L1 antibodies (atezolimumab, durvalumab and avelumab) are approved for the treatment of various metastatic malignancies. The combination of CTLA-4 and PD-1 blockade shows improved clinical efficacy in melanoma, but results in significantly increased toxicity [10]. Inhibitors for additional immune checkpoints such as T cell membrane protein 3 (TIM3) [11], Lymphocyte-activation gene 3 (LAG3) [12] and

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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 fasciitis. 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 Welche'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 sinunasal 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 ACPA-positive patient, the development of seronegative oligoarthritis in a patient with a family history of psoriasis, new-onset fasciitis, 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 sinu-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 recurred upon tapering yet responded partially to the addition of MTX.

Table 1
Oncologic characteristics of patients with rheumatic iAEs.

Patient	Age/gender	Type of malignancy	Immunotherapy	Previous lines of therapy	Immune related AE/grade	Rheumatic AE/grade	Best overall response	Time to response	PFS	Overall survival
1	67/F	Melanoma	Pembrolizumab	N/A	Gastritis/2 Psoriasis/1 Hepatitis/3	Inflammatory arthritis/3	Mixed (SD)	5 m	26 m	28 m+
2	38/M	Melanoma	Pembrolizumab	N/A	Vitiligo/2 Hepatitis/1	Inflammatory arthritis/3	PR	3 m	26 m+	29 m+
3	62/M	Melanoma	Nivolumab	Ipilimumab	Pneumonitis/1 Colitis/1 Vitiligo/1	Inflammatory arthritis/2	Mixed (SD)	6 m	10 m	10 m
4	68/F	Melanoma	Ipilimumab + nivolumab	N/A	None	Inflammatory arthritis/2	PR	3 m	16 m	21 m+
5	45/M	Melanoma s/p Hodgkin's lymphoma	Pembrolizumab	Ipilimumab Temozolomide	None	Inflammatory arthritis/2	Mixed (SD)	3 m	4 m	Lost to follow-up
6	71/F	Melanoma s/p Breast	Nivolumab	N/A	Pneumonitis/2 Vitiligo	Inflammatory arthritis/3	PR	2 m	22 m+	22 m+
7	53/F	Melanoma	Pembrolizumab	N/A	None	Eosinophilic fasciitis/3	CR	3 m	28 m	29 m+
8	71/F	Melanoma	Pembrolizumab	N/A	None	Inflammatory arthritis/3	PR	1.5 m	41 m+	41 m+
9	66/F	Melanoma	Ipilimumab	N/A	Colitis/4 Fatigue/1	Inflammatory arthritis/2	N/A[a]	N/A[a]	29 m+	29 m+
10	66/M	Melanoma	Pembrolizumab	N/A	None	Inflammatory arthritis/3	PR	1.5 m	5 m+	5 m+
11	78/M	Melanoma	Nivolumab	N/A	Thyroiditis/1 Diabetes/2 Fatigue/1	Inflammatory arthritis/3	CR	3.5 m	27 m+	27 m+
12	54/F	Melanoma	Nivolumab	N/A	Pneumonitis/3 Fatigue/2	Sarcoidosis/2	CR	6 m	23 m+	23 m+
13	63/F	Endometrium	Pembrolizumab	N/A	None	Inflammatory arthritis/3	CR	3 m	22 m+	32 m+
14	53/M	Sinonasal	Pembrolizumab		Chemoradiation	Rash/1	Inflammatory arthritis/3	PR	9 m	24 m+
24 m+										

N/A – not applicable, PR – partial response, CR – complete response, SD - stable disease, PFS - progression free survival, NED – no evidence of disease.
[a] Treated as Stage IV NED after surgery.

The lag period until development of the rheumatic iAE in our series is seemingly far longer than the 7.3 weeks recently described by Calabrese et al. in their series of 13 patients from the Cleveland clinic [16] or the median of 3 months reported by Cappelli et al. in their series of 13 patients from Johns Hopkins [17]. However, closer scrutiny reveals that the melanoma patients developed arthritis in the Calabrese series at an average time of 23.5 weeks, and 13 months for the 3 melanoma patients in Cappelli's series. Taken together, it seems that inflammatory arthritis is a late iAE of ICIs in patients with melanoma, manifesting within 6–24 months of initiation of immunotherapy.

The long incubation period between initiation of immunotherapy and the development of arthritis in patients with melanoma alludes to a different mechanism underlying this autoimmune phenomenon from the hypophysitis, pneumonitis, colitis and rash which appear earlier in the treatment course. Moreover, whereas aside from hypophysitis which leads to chronic damage and the need for continuous hormonal replacement, the other iAE, if not fatal, resolve without long term sequela or the need for chronic therapy. Conversely, inflammatory arthritis tends to develop later in the course of immunotherapy, necessitates chronic immunosuppressive therapy for symptom control and in general, requires higher doses of steroids than in unprovoked rheumatoid or psoriatic arthritis. Patients in the Calabrese series received hydroxychloroquine, methotrexate and tumor necrosis factor inhibitors (TNFi) in order to overcome their arthritis. TNFi were also given to 4 of 9 patients with inflammatory arthritis in Cappelli's series. We were able to avoid TNFi therapy, perhaps due to the early initiation of methotrexate. As it is becoming clearer from the case series published thus far that arthritis developing on ICIs is a chronic condition, and realizing that ICIs dramatically improve the survival of what were previously terminally-ill patients, the long term consequences of anti-arthritis therapy should be taken into consideration. Specifically, the cancerogenic potential of the various immune modulating anti-arthritic therapies should be evaluated.

The role of TNF in melanoma is controversial. It was first characterized in the 1970s as a cytotoxic molecule for cancer cells [22]. When TNFi therapy was developed for RA in the 1990s, patients with a personal or family history of malignancy were excluded from clinical trials [23]. However, multiple recent reports have shown that TNF associated inflammation as well as its direct effects on tumor cells may actually be cancer promoting. In melanoma, preclinical models have shown that TNF can induce cell invasion and angiotropism, thus increasing the likelihood of hematogenous dissemination and dedifferentiation thereby impairing sensitivity to melanocyte-differentiation antigen (MDA)-directed $CD8^+$ immune responses and impairing accumulation of $CD8^+$ T cells in the tumor microenvironment [24]. TNF inhibition seems to prevent lung metastasis in animal models [25]. Most importantly, recently published registry data demonstrate that chronic treatment with TNFi does not increase the risk of developing melanoma in human subjects [26,27]. While this data may give us to necessary reassurance to treat patients with a history of melanoma with TNFi with a greater measure of confidence, it takes a great leap of faith to give long term TNFi to patients with active metastatic disease. The data regarding the safety of non-TNFi biologics in cancer is less extensive than for TNFi's hence at this time they cannot be considered a better alternative.

Disease modifying anti-rheumatic drugs (DMARDs), such as methotrexate, hydroxychloroquine, leflunomide and sulphasalazine, are not necessarily safer in patients with metastatic melanoma. Previously, a three-fold rate of invasive malignant melanoma was noted in RA patients treated with MTX for over a decade of treatment compared with the general population (standardized incidence ratio (SIR) 3, 95% confidence interval (CI) 1.2–6.2) [28]. However, in the collaborative effort of 11 European biologic registries mentioned above, no increased risk in the incidence of melanoma among patients who were TNF-naïve (SIR 1.1, 95% CI 0.9–1.4) and TNF experienced (SIR 1.2, 95% CI

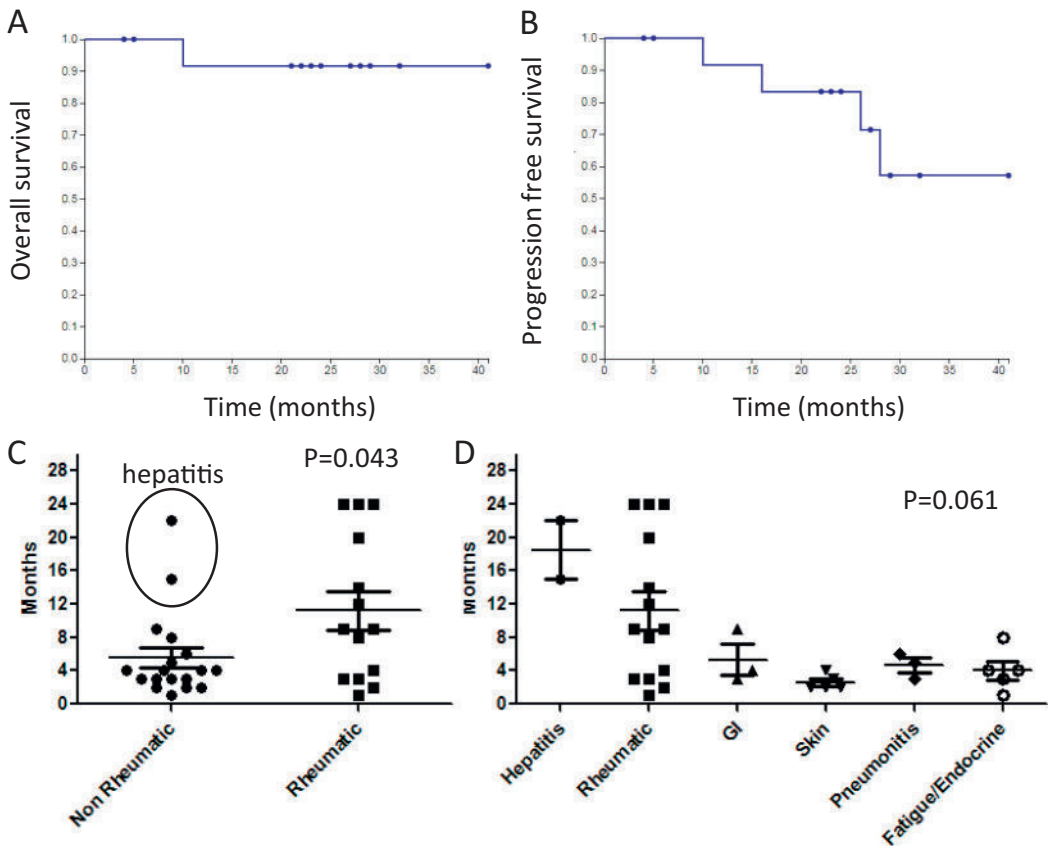

Fig. 1. Survival curves and onset of iAEs. (A) shows the overall survival; (B) shows the progression free survival of patients included in the study cohort. iAEs were divided into the depicted categories. In (C) all non-rheumatic iAEs are pooled together, which in (D) each iAE category is depicted. Each individual event is denoted. Y axis denotes the time from initiation of therapy. Horizontal lines denote the mean. Error bars denote standard error. Unpaired t-test with Welch's correction and Kruskal-Wallis tests were used in (A) and (B), respectively. The p values are indicated in the figure.

0.99–1.6) [26]. As MTX is the most commonly utilized DMARD, either as a single agent or in combination, among the TNF naïve group, it may be concluded that it holds the same risk for melanoma as TNFi therapy. To conclude, presently there are no reports regarding the safety of TNFi therapy in patients with active malignancy, specifically, metastatic malignant melanoma, although there is a substantial body of evidence to show there is no increase in the rate of malignancy associated with their use in clinical practice. Assuming TNFi therapy holds the same cancer risk as therapy with MTX or other DMARDs, their use is still associated with a higher incidence of serious infections compared to traditional disease modifying anti-rheumatic drugs (DMARDs) with an adjusted hazard ratio (HR) of 1.2 (95% CI 1.1 to 1.5) [29,30]. Assuming that the baseline infectious risk of patients with a malignancy, whether on or off immunotherapy, is no lower than that of patients with rheumatic diseases, it stands as a substantial obstacle to TNFi therapy in oncologic patients. Taken together with the more practical issue that TNFi therapy is far more expensive and typically reimbursed only after failure of one or two DMARDs, we suggest that MTX be the first treatment choice for steroid dependent patients with IA associated with ICI therapy. In our small case series it seems both safe and effective.

Data about use of DMARDs other than MTX (such as sulphasalazine, hydroxychloroquine or leflunomide) are limited to single case reports. Their onset of action is as slow as MTX's (4–8 weeks for a discernible clinical effect) and their efficacy no higher in patients with IA such as RA, bequeathing no added benefit. As for biologic agents other than TNFi, giving that they carry similar infectious risks to TNFi and that their safety in patients with an active malignancy is equally unknown, they offer no benefit over TNFi, which, at a minimum, have the track record of proving useful in other iAE of ICIs.

Interestingly, sicca syndrome was the rheumatic iAE in a third of the patients in the Calabrese and Cappelli series (9/26) together whereas it was not described in a single of our patients. This highlights the importance of multi-disciplinary clinics in which complaints of ocular and oral dryness shall be evaluated and treated. That being, as the diagnosis of sicca syndrome, in the two other series, was based on clinical impression supported by objective tests of dryness, but not on the presence of autoantibodies or a positive salivary gland biopsy, it is not improbable that it may have been an AE of therapy but not necessarily an iAE.

The first case of de-novo sarcoidosis developing following anti PD-1 therapy in a patient, who had attained complete remission, is included in our series. Here, a short course of steroids sufficed to control symptoms of dyspnea, arthralgia and hypercalcemia. Similar therapy was successfully instituted in a published case of a 72 year old woman who had suffered a flare of pre-existing sarcoidosis post anti PD-1 therapy for non-Hodgkin's lymphoma (NHL) [31]. Sarcoidosis is FDG avid on PET CT, mimicking the malignancy for which anti PD-1 is being used and thus may be falsely interpreted as tumor progression. A typical constellation of sarcoid symptoms and findings as described in our case, or a combination of hilar adenopathy, uveitis and skin nodules in the case reported in the literature, together with prompt response to steroids, suggests a diagnosis of sarcoid rather than of progressive disease.

Based on the 40 cases included in the present case series, together with the 2 previously published cases series [16,17] as well as on the systematic review of the literature published recently by Cappelli et al. [32], we have formulated screening questions, to be used by the oncologist, when assessing for side effects in patients on ICIs (Box 1). Should the answer to any of these questions be “yes”, or if the patient has a history of a rheumatic disease, the patient should undergo an evaluation by a rheumatologist including screening for the following autoimmune

Table 2
Characteristics of rheumatic irAE.

Patient	Rheumatic AE phenotype	Serology	Synovial fluid analysis/imaging/biopsy	Predisposing factor for rheumatic irAE	Time to onset of rheumatic irAE	Treatment	Immunotherapy	Follow up since onset of rheumatic AE	Current rheumatic disease/anti-rheumatic medication status
1	Polyarthritis	Negative	ND	Psoriasis	4 months	NSAIDS – IE Steroids - E	Continued	12 months	LDA/on
2	Oligoarthritis	Negative	ND	Family history of psoriasis	14 months	NSAIDS – IE Steroids – partial MTX – E	Off therapy	7 months	LDA/on
3	Polyarthritis	Negative	ND	None identified	9 months	NSAIDS – IE Steroids - E	Off therapy	11 months	LDA/on
4	Polyarthritis	Negative	ND	None identified	3 months	NSAIDS – IE Steroids – partial MTX – E	Continued	16 months	LDA/on
5	Polyarthritis	Negative	ND	None identified	3 months	NSAIDS – IE Steroids – partial	Withheld	24 months	Unknown
6	Polyarthritis	Negative	ND	None identified	9 months	NSAIDS - IE Steroids - E	Off therapy	18 months	Remission/off
7	Eosinophilic fasciitis	Negative	PET CT – increased uptake in soft tissues in legs Muscle biopsy – eosinophilic fasciitis	None identified	8 months	NSAIDS – IE Steroids – partial MTX – E	Off therapy	6 months	LDA/on
8	Polyarthritis	Negative	ND	uveitis	24 months	NSAIDS – IE Steroids – partial MTX - E	Off therapy	6 months	LDA/on
9	Monoarthritis	Negative	ND	None identified	12 months	NSAIDS – IE Steroids - E	Off therapy	3 months	Remission/off
10	Polyarthritis	Negative	Synovitis of hands joints and knees on US	Smoking	2 months	NSAIDS – IE Steroids – partial MTX - E	Withheld	3 months	LDA/on
11	Polyarthritis	Negative	Large and small joint involvement on PET CT	None identified	24 months	Steroids - effective at dose >20 mg/d MTX - E	Off therapy	3 months	LDA/on
12	Sarcoidosis	Negative	Hilar adenopathy, interstitial pulmonary infiltrates and hypercalcemia	None identified	24 months	Steroids - E	Off therapy	5 months	Remission/off
13	Polyarthritis	Negative	ND	None identified	20 months	NSAIDS – IE Steroids – E MTX-E	Withheld	8 months	LDA/on
14	Polyarthritis	ACPA	ND	Serology	1 month	Steroids – E MTX - E	Continued	24 months	Moderate/on

Negative serology: RF ACPA ANA – negative, E - effective, IE – ineffective, LDA – low disease activity, ND – Not done.

serologies (ANA, RF, anti SS-A, anti SS-B, ANCA and ASCA). If a diagnosis of iAE is established, we suggest initiating oral steroid therapy with the addition of methotrexate if the situation does not allow for rapid tapering or if a high initial steroid dose is needed to control symptoms. As rheumatic iAEs tend to follow a chronic course, the lowest possible steroid dose with the safest DMARD should be used. Due to the increased infectious risk associated with TNFi during their initial use, their questionable safety in people with active malignancy and the need for continuous therapy for rheumatic iAE, it may be more prudent to use biologic agents only as second line therapy in MTX failures.

Box 1

- Have you ever suffered from arthritis? Do you presently suffer from joint or muscle pain?
  - Do you suffer from dryness of eyes or mouth?
  - Do you have a personal or family history of psoriasis?
  - Have you ever had an episode of uveitis?
  - Have you recently started suffering from headaches or scalp tenderness? Do you have difficulty chewing? Do you experience difficulty lifting up your arms above shoulder level or getting up from a toilet seat?
  - Have you ever been told you have an abnormal chest radiograph?
  - Have you been diagnosed with inflammatory bowel disease (IBD)?

5. 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. Regular use of our proposed screening questionnaire should facilitate early referral and diagnosis with prompt initiation of effective therapy, preferably, without need to interrupt the immunotherapy schedule. We show that rheumatic manifestations appear later in the course of iAEs and respond preferentially to high dose steroids. MTX appears effective as a steroid sparing agent.

Conflict of interests

None.

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References

[1] Krummel MF, Allison JP. CD28 and CTLA-4 have opposing effects on the response of T cells to stimulation. J Exp Med 1995;182:459–65.
[2] Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisited. Annu Rev Immunol 2005;23:515–48.
[3] Khalil DN, Smith EL, Brentjens RJ, Wolchok JD. The future of cancer treatment: immunomodulation, CARs and combination immunotherapy. Nat Rev Clin Oncol 2016;13:273–90.
[4] Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711–23.
[5] Robert C, Thomas L, Bondarenko I, O'Day S, Weber J, Garbe C, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med 2011;364:2517–26.
[6] Eggermont AMM, Suciu S, Testori A. Ipilimumab adjuvant therapy in melanoma. N Engl J Med 2017;376:399.
[7] Cutolo M, Nadler SG. Advances in CTLA-4-Ig-mediated modulation of inflammatory cell and immune response activation in rheumatoid arthritis. Autoimmun Rev 2013;12:758–67.
[8] Okazaki T, Chikuma S, Iwai Y, Fagarasan S, Honjo T. A rheostat for immune responses: the unique properties of PD-1 and their advantages for clinical application. Nat Immunol 2013;14:1212–8.
[9] Zou W, Wolchok JD, Chen L. PD-L1 (B7-H1) and PD-1 pathway blockade for cancer therapy: mechanisms, response biomarkers, and combinations. Sci Transl Med 2016;8:328rv4.
[10] Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med 2015;373:23–34.
[11] Anderson AC. Tim-3: an emerging target in the cancer immunotherapy landscape. Cancer Immunol Res 2014;2:393–8.
[12] Woo SR, Turnis ME, Goldberg MV, Bankoti J, Selby M, Nirschl CJ, et al. Immune inhibitory molecules LAG-3 and PD-1 synergistically regulate T-cell function to promote tumoral immune escape. Cancer Res 2012;72:917–27.
[13] Markel G, Seidman R, Stern N, Cohen-Sinai T, Izhaki O, Katz G, et al. Inhibition of human tumor-infiltrating lymphocyte effector functions by the homophilic carcinoembryonic cell adhesion molecule 1 interactions. J Immunol 2006;177:6062–71.
[14] Ortenberg R, Sapir Y, Raz L, Hershkovitz L, Ben Arav A, Sapoznik S, et al. Novel immunotherapy for malignant melanoma with a monoclonal antibody that blocks CEACAM1 homophilic interactions. Mol Cancer Ther 2012;11:1300–10.
[15] Weber JS, Kahler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. J Clin Oncol 2012;30:2691–7.
[16] Calabrese C, Kirchner E, Kontzias K, Velcheti V, Calabrese LH. Rheumatic immune-related adverse events of checkpoint therapy for cancer: case series of a new nosological entity. RMD Open 2017;3:e000412.
[17] Cappelli LC, Gutierrez AK, Baer AN, Albayda J, Manno RL, Haque U, et al. Inflammatory arthritis and sicca syndrome induced by nivolumab and ipilimumab. Ann Rheum Dis 2017;76:43–50.
[18] Gianchecchi E, Delfino DV, Fierabracci A. Recent insights into the role of the PD-1/PD-L1 pathway in immunological tolerance and autoimmunity. Autoimmun Rev 2013;12:1091–100.
[19] Greisen SR, Yan Y, Hansen AS, Veno MT, Nyengaard JR, Moestrup SK, et al. Extracellular vesicles transfer the receptor programmed death-1 in rheumatoid arthritis. Front Immunol 2017;8:851.
[20] Turpin D, Truchetet ME, Faustin B, Augusto JF, Contin-Bordes C, Brisson A, et al. Role of extracellular vesicles in autoimmune diseases. Autoimmun Rev 2016;15:174–83.
[21] Sandigursky S, Silverman GJ, Mor A. Targeting the programmed cell death-1 pathway in rheumatoid arthritis. Autoimmun Rev 2017;16:767–73.
[22] Carswell EA, Old LJ, Kassel RL, Green S, Fiore N, Williamson B. An endotoxin-induced serum factor that causes necrosis of tumors. Proc Natl Acad Sci U S A 1975;72:3666–70.
[23] Maini R, Clair EW St, Breedveld F, Furst D, Kalden J, Weisman M, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. Lancet 1999;354:1932–9.
[24] Donia M, Kjeldsen JW, Svane IM. The controversial role of TNF in melanoma. Oncoimmunology 2016;5:e1107699.
[25] Orosz P, Echtenacher B, Falk W, Ruschoff J, Weber D, Mannel DN. Enhancement of experimental metastasis by tumor necrosis factor. J Exp Med 1993;177:1391–8.
[26] Mercer LK, Askling J, Raaschou P, Dixon WG, Dreyer L, Hetland ML, et al. Risk of invasive melanoma in patients with rheumatoid arthritis treated with biologics: results from a collaborative project of 11 European biologic registers. Ann Rheum Dis 2017;76:386–91.
[27] Giat E, Ehrenfeld M, Shoenfeld Y. Cancer and autoimmune diseases. Autoimmun Rev 2017;16:1049–57.
[28] Buchbinder R, Barber M, Heuzenroeder L, Wluka AE, Giles G, Hall S, et al. Incidence of melanoma and other malignancies among rheumatoid arthritis patients treated with methotrexate. Arthritis Rheum 2008;59:794–9.
[29] Minozzi S, Bonovas S, Lytras T, Pecoraro V, Gonzalez-Lorenzo M, Bastiampillai AJ, et al. Risk of infections using anti-TNF agents in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: a systematic review and meta-analysis. Expert Opin Drug Saf 2016;15:11–34.
[30] Ramiro S, Sepriano A, Chatzidionysiou K, Nam JL, Smolen JS, van der Heijde D, et al. Safety of synthetic and biological DMARDs: a systematic literature review informing the 2016 update of the EULAR recommendations for management of rheumatoid arthritis. Ann Rheum Dis 2017;76:1101–36.
[31] Cotliar J, Querfeld C, Boswell WJ, Raja N, Raz D, Chen R. Pembrolizumab-associated sarcoidosis. JAAD Case Rep 2016;2:290–3.
[32] Cappelli LC, Gutierrez AK, Bingham III CO, Shah AA. Rheumatic and musculoskeletal immune-related adverse events due to immune checkpoint inhibitors: a systematic review of the literature. Arthritis Care Res 2017;69(11):1751–63 November 2017.