RMD Open
Rheumatic & Musculoskeletal Diseases

CLINICAL CASE

Rheumatic immune-related adverse events of checkpoint therapy for cancer: case series of a new nosological entity

C Calabrese,[1,2] E Kirchner,[1,2] A Kontzias,[1,2] V Velcheti,[1,3] L H Calabrese[1,2]

To cite: Calabrese C, Kirchner E, Kontzias A, *et al*. Rheumatic immune-related adverse events of checkpoint therapy for cancer: case series of a new nosological entity. *RMD Open* 2017;**3**: e000412. doi:10.1136/rmdopen-2016-000412

► Prepublication history and additional material for this paper is available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/rmdopen-2016-000412).

Received 21 November 2016
Revised 19 January 2017
Accepted 5 February 2017

[1]Cleveland Clinic Foundation, Cleveland, Ohio, USA
[2]Department of Rheumatology and Immunology, Cleveland Clinic, Cleveland, Ohio, USA
[3]Department of Hematology and Oncology, Cleveland Clinic, Cleveland, Ohio, USA

Correspondence to
Dr Leonard H Calabrese; calabrl@ccf.org

ABSTRACT

Immunotherapy of cancer with checkpoint inhibitors has been associated with a spectrum of autoimmune and systemic inflammatory reactions known as immune-related adverse events (irAEs). Rheumatic irAEs are infrequently reported and extensively described. Here, we report our experience over an 18-month period with 15 patients evaluated in the rheumatology department for rheumatic irAEs. We identified 13 patients without pre-existing autoimmune disease (AID) who subsequently developed rheumatic irAEs, and two with established AID referred pre-emptively. irAEs encountered included: inflammatory arthritis, sicca syndrome, polymyalgia rheumatica-like symptoms and myositis. All cases required glucocorticoids, and three required a biological agent. Rheumatic irAEs led to temporary or permanent cessation of immunotherapy in all but five patients. One patient with pre-existing AID experienced a flare after starting immunotherapy. Our findings underscore that rheumatic irAEs are complex, at times require additional immunosuppressive therapy, and may influence ongoing immunotherapy regimens for the primary disease. Similar irAEs will be increasingly seen as checkpoint inhibitors adopted as standard of care in the community.

INTRODUCTION

The introduction of biological agents targeting immunological checkpoints represents a major advance in the field of oncology. At the present time, there are four Food and Drug Administration (FDA)-approved drugs: ipilimumab, targeting cytotoxic T-lymphocyte-associated protein (CTLA-4), nivolumab and pembrolizumab, targeting programmed cell death protein 1 (PD-1), and atezolizumab which targets programmed cell death ligand 1 (PD-L1). These medications have produced significant survival benefits in patients with metastatic melanoma, non-small cell lung cancer, renal cell carcinoma, Hodgkin lymphoma and urothelial carcinoma and are in investigation for many others. Many other targets for checkpoint therapy are now in clinical trials.[1]

Checkpoint inhibitors exploit suppressor and regulatory pathways, thereby boosting integrated immunity against tumours. Unfortunately, these new therapies are attended by a unique spectrum of immune-related adverse events (irAEs) related to overactivation of the immune system with resultant autoimmune disease (AID). The most commonly affected systems are the dermatological, gastrointestinal and endocrine. Reports of rheumatic irAEs have been sparse, not systematically reported, and have only been described in case reports or small series. These adverse events have recently been described in what was the largest case series to date.[2] Most clinical trials for immunotherapy agents do not report on the rheumatic manifestations and have excluded patients with pre-existing AID.[3]

At our institution, we created a multidisciplinary referral process to evaluate and manage irAEs. In this article, we report a series of patients evaluated at the Cleveland Clinic Foundation from 2015 to 2016 with rheumatic irAEs as a result of immunotherapy, as well as patients with pre-existing rheumatic AID who were evaluated pre-emptively.

METHODS

In February 2016, an interdisciplinary group was created at the Cleveland Clinic Foundation to manage irAEs occurring in patients on approved and experimental immune-based therapies for cancer. Patients were identified by the treating oncologist and then triaged by a designated advanced practitioner and seen in a facilitated fashion. Two designated rheumatologists saw all patients referred to the rheumatology arm of the multidisciplinary clinic. Two types of referrals were made: (1) patients without pre-existing AID who developed a rheumatic

RMD Open: first published as 10.1136/rmdopen-2016-000412 on 20 March 2017. Downloaded from http://rmdopen.bmj.com/ on December 3, 2020 by guest. Protected by copyright.

irAE after start of immunotherapy and (2) patients with pre-existing AID referred for pre-emptive evaluation. Patients were determined to have no pre-existing AID based on no prior diagnosis in their medical record, as well as through history taking during clinic visits with the treating rheumatologist. All patients were over the age of 18 and receiving or scheduled to receive ipilimumab, nivolumab, tremelimumab (anti-CTLA-4), durvalumab (anti-PD-L1) or atezolizumab either as monotherapy or in combinations. Patients were classified as having sicca syndrome, polymyalgia rheumatica (PMR)-like symptoms, inflammatory arthritis or myositis based on history, examination, imaging and laboratory findings as determined by the treating rheumatologist.

All patients were included in a database of information culled from the electronic medical record including: gender, date of birth, age at diagnosis of malignancy, type and stage of malignancy, prior treatment (chemotherapy, radiation, surgery), checkpoint inhibitor (drug(s), date started, date of last dose), pre-existing autoimmune history, nosology of irAE (type, date of onset, diagnostic testing), irAE treatment and global response to treatment, and prior autoimmune serology. Response was clinically defined as significant on near-complete resolution of rheumatic irAE symptoms, moderate on improvement to the point that symptoms were tolerable but still present and minimal if symptoms remained severe despite treatment.

RESULTS

Demographics

Rheumatic irAEs were evaluated in 15 patients between February 2015 and September 2016. Thirteen patients without pre-existing rheumatic AID were referred to our rheumatology department for evaluation after onset of irAE. Two patients with established AID (one rheumatoid arthritis, one psoriatic arthritis) were evaluated pre-emptively prior to starting immunotherapy. In the entire group, the median age was 63 years and 67% were male. The most common malignancy was melanoma (seven), followed by non-small cell lung cancer (four) and renal cell carcinoma (four) (table 1). All had been previously treated with surgery, chemotherapy, radiation or a combination of two or all three treatments. Seven patients received combination therapy with ipilimumab and nivolumab, one patient received tremelimumab followed by durvalumab, one received ipilimumab followed by pembrolizumab, and the remaining six received monotherapy with either nivolumab (five) or atezolizumab (one). Patients were receiving immunotherapy as standard of care and as participants in clinical trials.

No pre-existing autoimmune disease

In the group without AID (n=13) the median age was 63 years with median age at diagnosis of malignancy of 58 years. Rheumatic irAEs included seven patients with inflammatory arthritis, three with PMR-like syndrome, five with sicca syndrome and one with myositis. The majority of patients had more than one irAE (table 2) with patient 10 experiencing irAEs involving five different systems. Patients with arthritis exhibited different clinical phenotypes with the majority having a combination of small and large joint involvement (table 3). Regarding the patients with a PMR-like phenotype, all three had clinical features consistent with PMR including pain and stiffness involving the shoulders, hips/lower extremities and neck with associated severe morning stiffness. Two of the three had elevated inflammatory markers, and the third had normal inflammatory markers but levels had not been checked prior to initiation of prednisone to treat these symptoms. None had symptoms concerning for giant cell arteritis. Four of the five patients with sicca syndrome were xerostomic without keratoconjunctivitis. ANA was positive in two of the five, and SSA was positive in one (table 1). One sicca patient had a Schirmer's test performed, which was negative, and none underwent minor salivary gland biopsy. The myositis patient presented with proximal muscle weakness with diaphragmatic dysfunction, diplopia and dysphagia all attributable to myositis. Testing confirmed respiratory neuromuscular dysfunction and absence of primary oesophageal peristalsis. Electromyogram was consistent with severe inflammatory/necrotising myopathy. Imaging evaluation in our cohort was limited, but patient 11 did have a shoulder MRI to evaluate PMR symptoms which revealed extensive rotator cuff tendinosis and bursitis.

With the exception of two patients who experienced irAEs over 1 year after starting immunotherapy, the median time to onset of irAE was 7.3 weeks (range 2–48.4). The longest time between start of immunotherapy and development of irAE was 213 weeks in a patient who developed a PMR-like syndrome after over 4 years on nivolumab for renal cell carcinoma. Rheumatic irAEs led to holding of immunotherapy in eight patients and immune-related hypophysitis led to cessation of therapy in two of the remaining patients. Autoimmune testing was performed in the majority of patients (table 1). Four patients had a positive ANA with one also having anti-double stranded DNA antibodies and another anti-SSA antibodies. One patient with inflammatory arthritis was positive for rheumatoid factor (RF) but negative for anti-cyclic citrullinated protein antibodies. Eleven patients were treated with glucocorticoids for their rheumatic irAE; five required additional therapy with either anti-tumour necrosis factor (TNF) α medications, intravenous immunoglobulin or hydroxychloroquine. Treatment of irAEs led to significant improvement in six patients, moderate improvement in five patients and only minimal improvement in two. Non-rheumatic irAEs (table 2) were addressed per guidelines on an individualised basis.

Patients with pre-existing autoimmune disease

Of the two patients with pre-established AID, one experienced a disease flare after starting immunotherapy: a patient with psoriatic arthritis previously treated with

RMD Open: first published as 10.1136/rmdopen-2016-000412 on 20 March 2017. Downloaded from http://rmdopen.bmj.com/ on December 3, 2020 by guest. Protected by copyright.

Table 1 Demographic features, cancer types, immunotherapy and rheumatic immune-related adverse events (irAEs)

Patient	Age	Sex	Malignancy	Immunotherapy	irAE	Serology	Time to onset (weeks)	Treatment	Improvement	Immunotherapy held for irAE
1	74	F	NSCL	Nivolumab	Arthritis	ANA 1:160 Anti-dsDNA 77	7.3	Prednisone 40 mg	Significant	Y
2	49	F	Melanoma	Ipilimumab Pembrolizumab	Arthritis		52.7	Prednisone 20 mg HCQ	Moderate	Y
3	42	F	RCC	Ipilimumab/ nivolumab	Arthritis		3	Prednisone Infliximab, MTX Etanercept	Moderate	N
4	57	M	RCC	Ipilimumab/ nivolumab	Arthritis	RF 214	48.4	Prednisone MTX Etanercept Adalimumab	Significant	N
5	59	F	Melanoma	Ipilimumab/ nivolumab	Arthritis		21.7	Prednisone 60 mg	Minimal	N
6	81	M	Melanoma	Ipilimumab/ nivolumab	Arthritis	ANA 1.5	13.1	Prednisone 15 mg	Moderate	Y
7	57	F	Melanoma	Ipilimumab/ nivolumab	Arthritis Sicca	ANA 1:320	6.7	Prednisone 30 mg	Significant	Y
8	61	M	Melanoma	Ipilimumab/ nivolumab	Sicca		5.3	Prednisone 60 mg*	Significant	Y†
9	63	M	RCC	Atezolizumab	Sicca		21.9	Prednisone 60 mg*	Significant	Y†
10	68	M	Melanoma	Ipilimumab/ nivolumab	Sicca PMR	ANA 1:1280 SSA	8.1	Prednisone 30 mg	Significant	Y
11	79	M	Melanoma	Nivolumab	PMR Sicca		2	Prednisone 20 mg	Moderate	Y
12	63	M	RCC	Nivolumab	PMR		213	Prednisone 40 mg Infliximab	Minimal	Y
13	68	M	NSCL	Tremelimumab Durvalumab	Myositis		4.6	IV methylpred Prednisone 60 mg	Moderate	Y

*Prednisone given for hypophysitis.
†Immunotherapy held for hypophysitis.
Atezolizumab, anti-PD-L1; durvalumab, anti-PD-L1; HCQ, hydroxychloroquine; MTX, methotrexate; NSCL, non-small cell lung cancer; PMR, polymyalgia rheumatica; RCC, renal cell carcinoma; RF, rheumatoid factor; tremelimumab, anti-CTLA-4.

RMD Open: first published as 10.1136/rmdopen-2016-000412 on 20 March 2017. Downloaded from http://rmdopen.bmj.com/ on December 3, 2020 by guest. Protected by copyright.

Table 2 Non-rheumatic immune-related adverse events (irAEs)

Patient	Non-rheumatic irAE
2	Hypothyroid
4	Colitis
5	Rash
	Hypothyroid
	Colitis
8	Hypophysitis
	Thyroiditis
9	Hypophysitis
10	Hypophysitis
	Pneumonitis
	Neuropathy
11	Hypophysitis
12	Colitis

apremilast had experienced remission of his psoriatic arthritis (PsA) while on chemotherapy. He experienced a psoriasis flare 2.8 weeks after starting nivolumab and apremilast was resumed. He experienced mild psoriasis flares on his face during therapy but inflammatory arthritis remained quiet. The patient with rheumatoid arthritis had seropositive, non-erosive disease; he remained without disease activity on hydroxychloroquine throughout his course of immunotherapy.

DISCUSSION

irAEs of any type are common in patients receiving immunotherapy, occurring in up to 90% of patients receiving anti-CTLA-4 agents[4] and 70% of those receiving anti-PD-1/PD-L1 agents.[5 6] Somewhat lower rates of irAEs have been seen with anti-PD-1 agents, but incidence increases when they are used in combination with inhibitors of CTLA-4.[7] The most common irAEs are gastrointestinal, hepatic, endocrine and dermatological events.[7 8] Rheumatic irAEs, however, have been infrequently reported in clinical trials[9] and generally have been the subject of isolated case reports.[9] One single-centre case series of rheumatic irAEs was recently published, in which Cappelli *et al*[2] described inflammatory arthritis and sicca syndrome in 13 patients receiving nivolumab and/or ipilimumab.[2] In this report, they described nine patients who developed inflammatory arthritis; synovitis was confirmed by imaging in four. Overall, a variety of rheumatic manifestations have been described in these reports including arthralgia, inflammatory arthritis, sicca complex as well as rare reports of vasculitis, myositis and lupus. Our series of 15 patients now expands the description of rheumatic irAEs and describes a wider variety of rheumatic irAEs than seen in previous reports, including inflammatory arthritis, sicca syndrome, a PMR-like syndrome and myositis in patients receiving monotherapy and combination therapy with checkpoint inhibitors.

Table 3 Clinical phenotypes of inflammatory arthritis

Patient	Joint pattern	Symmetrical	Tenosynovitis
1	PIPs, MCPs, wrists, elbows, knees	Yes	
2	Generalised involvement of small hand joints	Yes	Yes
3	PIPs, MCPs, PIPs, elbows, knees, ankles, feet, toes	Yes	
4	PIPs, MCPs, ankles, knees	Yes	
5	PIPs, MCPs, wrists, knees	Yes	
6	Generalised involvement of small hand joints, wrists	Yes	
7	Generalised involvement of small hand joints, left knee	No	Yes

MCP, metacarpal phalangeal joints; PIP, proximal interphalangeal joint.

In our study, in 13 of 15 subjects the median time to onset of rheumatic irAE was 7.3 weeks after initiation of immunotherapy, which is consistent with previous reports. In clinical trials for ipilimumab, the majority of all irAEs have been reported to occur within 12 weeks of initial dosing, and this seems to be consistent across numerous studies.[4 7] Interestingly there were two outliers in our cohort with one patient developing a PMR-like syndrome after over 4 years of being stable on nivolumab. Reasons for the delay in irAE presentation are unknown. Several patients were noted to have persistent symptoms for months after immunotherapy was stopped. The longest persistence of symptoms in one patient was over 2 years after the last dose of immunotherapy. This persistence of rheumatic symptoms long after discontinuation of immunotherapy has also been previously described.[2]

The pathophysiology of each respective irAE remains to be fully elucidated albeit it seems that they are at least partially T cell-mediated as expected by the mechanism of action of these medications.[10] To date, there have been no detailed pathophysiological studies investigating the mechanism of any rheumatic irAE.

Management of rheumatic irAEs remains an area of uncertainty. In general, irAEs have been reported to be steroid sensitive and in most cases resolve within 6–12 weeks.[8] While some patients in our series were responsive to glucocorticoids, three out of 13 required more aggressive immunosuppression with TNF inhibitors. We also observed that these patients required higher doses of glucocorticoids and largely more intense therapy than our traditional experience with inflammatory arthritis seen in rheumatoid arthritis or associated with connective tissue disease.

RMD Open: first published as 10.1136/rmdopen-2016-000412 on 20 March 2017. Downloaded from http://rmdopen.bmj.com/ on December 3, 2020 by guest. Protected by copyright.

An important clinical question is whether patients with pre-existing rheumatic diseases undergoing cancer immunotherapy with checkpoint inhibitors are at increased risk for flares of their underlying diseases. The largest series to date describes 30 patients with pre-existing AIDs of a variety of sorts; eight experienced flares 3 days to 7 months after starting ipilimumab.[11] In our study, one of two patients experienced a flare of underlying AID. The patient had psoriatic arthritis and the flare was managed with apremilast without interruption of immunotherapy. In our entire cohort, treatment discontinuation rate owing to irAEs was significantly higher (10 of 13 patients) compared with the literature. Immunotherapy was discontinued for rheumatic irAEs in eight of the 10, and for endocrine irAE in two patients. This needs to be validated in larger prospective cohort trials.

A comprehensive grading system for rheumatic irAEs is lacking as opposed to other more common irAEs. Additionally, despite a standardised grading system, toxicity evaluation and treatment for all irAEs is highly subjective based on the treating oncologist.[9] Incorporating rheumatic irAEs in the grading system of adverse effects of immunotherapy would facilitate early recognition, referral and expeditious management which may translate to decreased need for immunosuppressive medications and/or cessation of immunotherapy. It would also allow a more accurate assessment of the incidence and prevalence of these complications. New-onset inflammatory symptoms pertaining to the broad spectrum of rheumatological conditions postadministration of immune checkpoint inhibitors should be further investigated.

There are several limitations of our study. While our series is the largest to date, it is a single-centre experience and retrospective in nature. Accordingly diagnostic testing, including laboratory tests, imaging and organ-specific testing, was not standardised and thus subject to diagnostic bias. For those patients who did have positive tests (ie, ANA, RF, etc), there was no testing prior to immunotherapy for comparison. There was limited use of imaging and no synovial fluid analysis to confirm inflammatory arthritis. All rheumatic irAE diagnoses were based on expert opinion of the rheumatologist. We also were unable to determine the true incidence of rheumatic irAEs given the observational basis of this cohort.

At present, it is clear that we are in the early stages of diagnosing and treating rheumatic irAEs secondary to immunotherapy of cancers with checkpoint inhibitors. Numerous questions are unanswered regarding these complications. These questions include: what is the true incidence of these disorders with individual and combined therapies? What are the risk factors and what is the underlying pathophysiology of these disorders? What are the risks of disease flare with these types of immunotherapy in patients with pre-existing autoimmune conditions? In terms of therapy, what is the optimal treatment of these types of complications and finally what are the ramifications of concomitant immunosuppressive therapy for irAEs on antitumorous responses? Given the proliferation of checkpoint inhibitor therapy into the general oncology armamentarium and the rise of new therapeutics with similar mechanisms of action, it is assured that rheumatic adverse events will be seen by general rheumatologists in academic and community settings. Rheumatologists must be alerted to these complications and acquire knowledge to accurately diagnose and manage these disorders in collaboration with treating oncologists.

Correction notice This article has been corrected since it first published. The third author of this paper should be cited as 'Kontzias A'.

Twitter Follow cassandra calabrese @CCalabreseDO

Contributors All authors contributed to data acquisition, analysis and manuscript preparation.

Competing interests LHC reports personal fees from Bristol-Myers Squibb, outside the submitted work. VV reports grants and personal fees from Bristol-Myers Squibb, grants and personal fees from Genentech, grants and personal fees from Merck, grants and personal fees from Astra Zeneca, personal fees from Celgene, grants and personal fees from Genoptix, personal fees from Foundation medicine, outside the submitted work. CC, KK and EK have nothing to disclose.

Ethics approval Cleveland Clinic Foundation IRB.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

REFERENCES

1. Topalian SL, Drake CG, Pardoll DM. Immune checkpoint blockade: a common denominator approach to cancer therapy. *Cancer Cell* 2015;27:450–61.
2. Cappelli LC, Gutierrez AK, Baer AN, *et al*. Inflammatory arthritis and sicca syndrome induced by nivolumab and ipilimumab. *Ann Rheum Dis* 2017;76:43–50.
3. Donia M, Pedersen M, Svane IM. Cancer immunotherapy in patients with preexisting autoimmune disorders. *Semin Immunopathol* 2016. Published Online First 11 October 2016. .
4. Hodi FS, O'Day SJ, McDermott DF, *et al*. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med* 2010;363:711–23.
5. Topalian SL, Hodi FS, Brahmer JR, *et al*. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med* 2012;366:2443–54.
6. Brahmer JR, Tykodi SS, Chow LQM, *et al*. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N Engl J Med* 2012;366:2455–65.
7. Boutros C, Tarhini A, Routier E, *et al*. Safety profiles of anti-CTLA-4 and anti-PD-1 antibodies alone and in combination. *Nat Rev Clin Oncol* 2016;13:473–86.
8. Michot JM, Bigenwald C, Champiat S, *et al*. Immune-related adverse e vents with immune checkpoint blockade: a comprehensive review. *Eur J Cancer* 2016;54:139–48.
9. Horvat TZ, Adel NG, Dang TO, *et al*. Immune-related adverse events, needs for systemic immunosuppression, and effects on survival and time to treatment failure in patients with melanoma treated with ipilimumab at Memorial Sloan Kettering Cancer Center. *J Clin Onc* 2015;33:3193–8.
10. Johnson DB, Balko JM, Compton ML, *et al*. Fulminant myocarditis with combination immune checkpoint blockade. *N Engl J Med* 2016;375:1749–55.
11. Johnson DB, Sullivan RJ, Ott PA, *et al*. Ipilimumab therapy in patients with advanced melanoma and preexisting autoimmune disorders. *JAMA Oncol* 2016;2:234–40.

RMD Open: first published as 10.1136/rmdopen-2016-000412 on 20 March 2017. Downloaded from http://rmdopen.bmj.com/ on December 3, 2020 by guest. Protected by copyright.

Correction: Rheumatic immune-related adverse events of checkpoint therapy for cancer: case series of a new nosological entity

Calabrese C, Kirchner E, Kontzias K, *et al*. Rheumatic immune-related adverse events of checkpoint therapy for cancer: case series of a new nosological entity. *RMD Open* 2017;3:e000412.

This article has been corrected since it first published. The third author of this paper should be cited as 'Kontzias A'.

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

© Article author(s) (or their employer(s) unless otherwise stated in the text of the article) 2017. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

RMD Open 2017;**0**:e000412corr1. doi:10.1136/rmdopen-2016-000412corr1