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A Case Series of Rheumatic Immune-Related Adverse Events in Patients with Immune Check Point Inhibition

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Abstract

Background: Immune check point inhibitors (ICIs) have a potent anti-tumour effect and up to 43% of people receiving therapy will develop rheumatic adverse effects (RirAEs). People with pre-existing autoimmune disease (AID) were excluded from clinical trials.

Aim: To define the characteristics of rheumatic symptoms in people on ICIs for malignancy and subsequent prescribed immunosuppression to manage adverse events.

Methods: A case series formed from a retrospective audit of the Northern Territory Top End Health Service electronic records over a two year period, 2016-2017.

Results: Sixty-three people received ICIs over the two year period for non-small cell lung carcinoma, melanoma and renal cell carcinoma. One patient had confirmed pre-existing rheumatoid arthritis and a further two had likely undiagnosed inflammatory arthritis preceding therapy. Sixteen (25%) patients developed RirAEs with nine requiring simple analgesia, glucocorticoids or biologic therapy. The autoimmunity phenotype was predominantly joint related, seronegative and polyarticular in nature. Five required alterations to immunotherapy and six were referred to rheumatology.

Conclusion: A significant number of people receiving ICIs will develop RirAEs, with arthritis and myalgia occurring most commonly. People with pre-existing AID remain a challenge to treat. Vigilant monitoring and early referral to a rheumatology service will facilitate appropriate investigations and encourage early treatment if required.

Keywords: Immunotherapy; Autoimmunity; Arthritis; Rheumatoid; Rheumatology; Glucocorticoids

Introduction

Immune checkpoint inhibitors (ICIs) are becoming an increasingly important therapy for a range of malignancies. While having a potent efficacy, patients may develop immune-related adverse events (irAEs). Few studies have systematically reported specific rheumatological and musculoskeletal adverse events and a standardized approach to management is required.

Cappelli et al. performed a literature review of MEDLINE and the CENTRAL database identifying the prevalence of rheumatic and musculoskeletal immune symptoms in patients on ICIs. Across 33 clinical trials, 1%-43% experienced arthralgia and 2%-20% myalgia [1]. One observational study described patients with pre-existing auto-immune diseases (AIDs) treated with ICIs [2]. While patients with pre-existing autoimmune diseases were excluded from clinical trial, clinicians are gaining experience in this field [3]. There is little data on the prevalence of synovitis, vasculitis and sicca syndrome.

Kostine et al. performed a prospective observational study of 524 patients receiving ICIs and found 35 (6.6%) developed rheumatic immune symptoms. Nineteen required treatment with glucorticoids, two required methotrexate and one required cessation of immunotherapy [4].

The checkpoint inhibitors that are currently available can block the proteins programmed death-1 (PD-1), programmed death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated antigen (CTLA-4). The three agents used in the Top End of the Northern Territory in 2016 and 2017 were ipilimumab, pembrolizumab and nivolumab.

Case Presentation

This retrospective audit captured all patients aged 18 years and older treated with ipilimumab, pembrolizumab, nivolumab or with the combination of ipilimumab and nivolumab in the TEHS between 1st January 2016 to the 1st February 2018.

The type of immunotherapy administered, cumulative doses, all irAEs reported, time to onset and type of rheumatic irAE, treatment required and continuation of ICI were assessed retrospectively from electronic patient notes. Patient progress was assessed at scheduled oncology clinics, various specialty clinics and inpatient admissions to

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Royal Darwin Hospital.

Baseline characteristics for age, sex, malignancy and pre-existing rheumatological disease were collected.

The primary outcome was the development of rheumatic adverse events identified by clinical, serological, and radiological means as assessed by any patient care provider.

RirAEs were defined as arthralgia, inflammatory arthritis, myalgia, myositis, sicca symptoms, lupus, psoriasis and vasculitis. Time to onset was taken from the first documentation of the irAE. If the particular patient was not seen by a rheumatologist to confirm the diagnosis of inflammatory arthritis, a provisional diagnosis was made based on the documented description of patient signs and symptoms if they met the majority of the following: joint pain, swelling, tenderness, erythema, early morning stiffness persisting for greater than thirty minutes, arthralgia worsens with inactivity and improves with exercise, NSAIDs and corticosteroids and symptoms persisting for several weeks without a plausible alternate diagnosis such as osteoarthritis or gout. All available pathology results were reviewed for ANA, dsDNA, ENA, RF, anti-CCP, CRP, ESR and joint aspirates and imaging assessed for targeted X-rays, ultrasounds, PET and MRIs performed.

The secondary outcomes assessed treatment required for rheumatic RirAE. Specifically, the prescription of non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, disease-modifying antirheumatic drugs (DMARDs) or biologics. ICI were either continued, temporarily withheld, ceased or changed to an alternate agent.

Low risk ethics approval was obtained through the Menzies School of Health Research reference number 2018-3117.

Results

Between January 2016 and January 2018, 63 patients received ICIs in the Top End Health Service TEHS and were included in the study. Patients received anti-PD-1 (n=54), a combination or sequential administration of anti-PD1 and CTLA-4 (n=8) or where part of the BMS CA209-915 trial (nivolumab or nivolumab and ipilimumab, n=1). A total of 525 cycles of ICI were administered over the two year period (Figure 1).

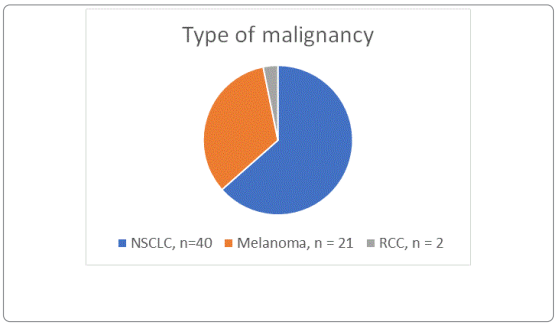

Figure 1: Cancer types included melanoma (n=21), lung cancer (n=40) and renal cell carcinoma (n=2).

After initiation of immunotherapy 16 patients developed rheumatic symptoms, with one having pre-existing rheumatoid arthritis RA, one with hand deformities consistent with a prior undiagnosed inflammatory arthropathy and one with a preceding history of undiagnosed inflammatory arthritis. Patients were not routinely assessed prior to commencement of ICIs for the rheumatic disease. Of the 16 affected patients, the mean exposure to ICIs to onset of symptoms was 6.5 months (range 0.75 to 24), the mean age was 56 years old (range 38-69) and 12 out of 16 were male.

The most common rheumatological RirAE were arthralgia (n=5), inflammatory arthritis (n=8) and myalgia (n=3). The phenotype of inflammatory arthritis was varied with five having polyarticular manifestations and three oligoarticular with predominant small and medium joint involvement. Other musculoskeletal symptoms included olecranon bursitis and shoulder adhesive capsulitis in one patient and sicca symptoms in another. Autoimmune serology was performed in four patients, besides rheumatoid factor and anti-CCP positivity in the patient with known seropositive rheumatoid arthritis (RA) the other three were negative. Seven patients had imaging performed including ultrasound, MRI, bone scan and PET scan. Specialist rheumatology opinion was sought in six cases.

Symptomatic treatment included paracetamol (n=2), NSAIDs (n=4), intra-articular steroid injection (n=2), prednisolone (n=9), infliximab (n=1) and rituximab (n=1). Five patients had immunotherapy withheld for varying periods of time with two recommencing ICI therapy. Only two patients had the ICI withheld specifically for rheumatological complications whereas three had the ICI withheld in the context of other associated ICI adverse events.

Of the patients with RirAEs, 11 also had other system irAEs documented with varying organ involvement and severity.

Two patients had aggressive synovitis refractory to high dose glucocorticoid treatment. The patient with pre-existing RA had previously required treatment with methotrexate and etanercept which were ceased once the diagnosis of melanoma was established. Synovitis developed six months later requiring NSAIDs, moderate to high dose glucocorticoid use and two courses of rituximab eight months apart with a good response. Synovitis subsequently flared and remained difficult to control despite further rituximab and high dose glucocorticoids during four cycles of pembrolizumab, subsequent tumour progression, four cycles of ipilimumab with good tumour response and subsequent tumour progression and rechallenge with ipilimumab. The second patient developed florid synovitis three weeks after the first dose of ICI with persistent symptoms despite regular NSAID use and repeated intra-articular (IA) steroid injections. After several months, ICI was ceased and immune suppression was escalated to high dose glucocorticoids and glucocorticoids then infliximab was prescribed with some clinical improvement but persisting polyarthralgia impairing patient mobility and quality of life (Table 1).

Discussion

In this cohort, ICI related autoimmunity was predominantly joint related with an oligo- and polyarticular and male sex predominance. It was largely seronegative without erosions on the limited imaging requested. Many of the cases were treated based on clinical grounds without supportive biochemical or radiological changes. While dedicated imaging was limited, surveillance PET scans detected joint uptake indicating underlying joint pathology in some cases.

While it is difficult to prove causality with small study numbers and without knowing the true background TEHS population prevalence and incidence of rheumatic symptoms in the eclectic Top End Health Service population, I have captured all musculoskeletal symptoms such as adhesive capsulitis and bursitis as this is a real life study. The treating clinician needs to knowledgeable and equipped with the tools to allow differentiation between inflammatory and non-inflammatory cases of musculoskeletal conditions to appropriately address patients' needs.

Joint disease tends to differ to the progressive and destructive nature of RA with most patients in this cohort had a good response to glucocorticoids with subsequent weaning to a low dose however a

Patient	Age	Sex	Malignancy	Immunotherapy	Total doses ICI	RirAE	Time to onset (months)	Other irAEs	Serology	Imaging	Treatment	ICI alterations	Rheumatology review
1	59	M	Melanoma	Nivolumab+ ipilimubab	2	Arthralgia: Polyarticular	5	Rash, aseptic, meningitis, hepatitis	Negative ANA, ENA, RF and ACPA	PET: Elbow uptake, XRAYS: NAD	Simple analgesia, 5/12 high dose prednisolone for othe irAEs	Yes-WH for other irAE	Y
2	62	F	Lung-adenocaecinoma	Nivolumab	1	Arthralgia: Polyarticular	1	Diarrhoea	Nil	Nil	Prednisolone 10 mg/d	Unknown	N
3	61	M	Melanoma	Pembrolizumab	9	Inflammatory arthritis: Polyarticular, myalgia	5	G1 rash	Negative ANA, RF and ACPA	PET; Joint uptake	Prednisolone 25 mg/d	Yes-for 1/12	Y
4	38	F	Melanoma	Nivolumab+ ipilimubab	4	Inflammatory arthritis	7	G3 rash	Nil	Nil	Prednisolone 15 mg/d	Yes-other irAE	Y
5	38	M	Melanoma	Pembrolizumab+ ipilimubab	3	Inflammatory arthritis: Polyarticular	7	G3-4 Hepatitis, G2 colitis	CRP 124	Nil	Prednisolone 50 mg/d (for hepatitis)	Yes-other irAEs	N
6	57	M	Melanoma	Pembrolizumab	3	Inflammatory arthritis	Un-known: Months	Hepatitis	Negative ANA, Positive ANCA	Nil	Prednisolone 5 mg	Nil	N
7	65	M	Melanoma	Pembrolizumab+ ipilimubab	13	Inflammatory arthritis: Polyarticular	1	Nil	Positive RF and ACPA	Nil	NSAIDs, Rituximab × 3 prednisolone 50 mg, IA, IM	Yes-ceased	Y
8	66	M	Lung-adenocaecinoma	Nivolumab	6	Sicca	2	Adrenalitis	Nil	Nil	Nil	Nil	N
9	55	M	Lung-adenocaecinoma	Pembrolizumab	15	Arthralgia	2	G1 diarrhoea	Nil	Nil	Simple analgesia	No	N
10	54	F	Melanoma	Nivolumab+ ipilimubab	5	Arthralgia	17	G2 Hepatitis, eye erythema	Nil	Nil	Nil	NO (Yes for othe irAE)	N
11	52	M	Lung-adenocaecinoma	Nivolumab	17	Myalgia	3	Nil	Nil	XRAY: R femur mets	Nil	NO	N
12	57	M	Melanoma	Pembrolizumab	25	Arthralgia: OA	24	Nil	Nil	Nil	Nil	NO	N
13	58	F	Lung-adenocaecinoma	Nivolumab	7	Inflammatory arthritis: Oligoarticular	5	Nil	Nil	Ultrasound: Shoulder effusion	NSAIDs	NO	N
14	63	M	Lung-adenocaecinoma	Nivolumab	26	Myalgia, arthralgia kmees, synovitis R wrist	13	G1 rash	Nil	Ultrasound: Synovitis	Prednisolone 15 mg/d 5/7	Yes-2 weeks	N
15	69	M	Melanoma	Pembrolizumab	7	Olecranon bursitis, shoulder adhesive capsulitis	5	Nil	Nil	USS: Bursitis, XRAY: NAD	Nil	No	Y
16	48	M	Melanoma	BMS CA209-915 trial	Un-known	Inflammatory arthritis: Oligoarticular	0.75	Rash, thyroditis, hypophysitis	Negative ANA, dsDNA, ENA, ACPA, RF, CRP 28, ESR34	MRI+ Ultrasound; Synovitis	IA steroids, 75 mg oral prednisolone, NSAIDS, infliximab	No initially, eventually had to cease trial	Y

Table 1: Demographics, adverse events and outcomes.

longer follow up period would be prudent to ensure no progressive joint destruction does not ensue [5]. Study numbers are too small to ascertain risk factors for aggressive and prolonged synovitis however it's possible that patients with pre-existing AID, exposure to dual ICI therapy, continued ICI despite poorly controlled RirAEs and delayed immune suppression may be contributing factors.

Given the complex interplay between autoimmunity and tumour response, patients would benefit from regular monitoring for the development of RirAEs with a low threshold to investigate thoroughly and systematically without delay in commencing treatment. Two patients had ICIs withheld purely for a RirAE whereas the other four had irAE affecting other systems requiring interruption of immunotherapy. Early commencement of treatment may allow for earlier recommencement of ICIs.

Patients with pre-existing inflammatory arthritis remain a challenge to treat with ICIs for two reasons. The first is the tendency to cease immunosuppression once a malignancy is diagnosed predisposing to a flare in synovitis which is further exacerbated by the ability of ICIs to provoke autoimmunity. Another cohort of patients are likely to have low grade or undiagnosed inflammatory arthritis unmasked by commencing ICIs hence requiring a thorough baseline clinical and biochemical evaluation prior to commencing immunotherapy. A baseline clinical questionnaire enquiring about pre-existing features of autoimmunity may be performed by the patient or with the treating oncologist prompting baseline serology, inflammatory markers and targeted imaging and referral for a specialist rheumatologist assessment. See Appendix 1.

While inhibiting deactivation of T cells remains paramount to allow optimal tumour response, synovitis has a significant impact on a patient's quality of life. There may be a tendency for patients and clinicians to underreport RirAEs and there is possible predisposition to undertreat synovitis to avoid presumably compromising the upregulated host vs tumour response. Recent studies have confirmed that appropriate immune suppression targeting irAEs does not hinder the anti-tumor efficacy of ICIs and hence treatment should not be delayed [6,7]. While a large proportion of irAEs are managed with glucocorticoids, DMARDs and biologics can be utilised to avoid the adverse events associated with long term steroid use [7]. Prompt referral to a rheumatology specialist when RirAEs occur is encouraged and ensure timely treatment and to avoid irreversible musculoskeletal damage.

The case numbers in this audit are insufficient to link the development of RirAEs and cancer outcomes. A correlation between developing irAEs and specifically RirAEs and an objective response rate has been demonstrated however the clinical benefit of this is dubious given there is no change in progression free survival and irAEs are certainly not desirable given high rates of patient morbidity and mortality [4,6].

In this cohort, 16 patients out of 63 patients had a rheumatic adverse event. Eight had inflammatory arthritis and four polyarthralgia. The prevalence of RirAEs is much higher than the quoted of 6.6% with Kostine et al. which may due to less stringent inclusion criteria given the varied presentations and retrospective nature of this study [4].

Based on this audit, I have created a patient-based questionnaire; see Appendix 1, to be completed by all patients commencing immunotherapy at baseline then prior to every oncology clinic which routinely occurs on fortnightly to monthly basis. Patients can choose to continue to questionnaire on a monthly basis for up to 12 months post cessation of immunotherapy to detect late onset irAEs. The questionnaire is relatively short, written in plain English and family members can assist with the completion process. The form is reviewed on the same day of completion by the treating oncologist with the patients and is a tool to prompt discussion and early recognition of RirAEs as well as all other systems potentially affected by irAEs. While aiming to detect all RirAEs, the reverse side of the questionnaire focusses on joint-related symptoms and encourages the patient and oncologist perform an affected joint count and a basic framework for the oncologist to work through in terms of characterising of inflammatory arthritis, suggested investigations and appropriate management based on the "Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice" [8]. It is to be used as a prompting tool only and expert opinion and consulting the full guidelines is encouraged. If baseline rheumatic symptoms are evident or when grade two to four inflammatory arthritis is identified, a rheumatology referral is encouraged and a copy of the patient questionnaire can be attached to the referral form and assist in the triaging process.

My case series could be elaborated with a prospective cohort study involving both the rheumatology and oncology departments to further characterize and quantify RirAEs supported by a causality assessment tool such as the Naranjo Criteria to allow optimal treatment for patients suffering rheumatic symptoms on immunotherapy [9,10].

Conclusion

A new and varied phenotype of rheumatological disease is emerging with a range treatment options available. As an increasing number of patients are treated with ICIs for an ever-growing list of malignancies, there will be an increasing need for oncologists and rheumatologists to collaborate. Navigating the intricacies linked to manipulating the immune system and delicate balance between tolerance of self and autoimmunity will continue to produce interesting sequelae of rheumatic symptoms.

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