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# Polymyalgia rheumatica-like syndrome from checkpoint inhibitor therapy: case series and systematic review of the literature

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## ABSTRACT

**Objective** To assess whether the polymyalgia rheumatica (PMR)-like syndrome reported as an immune related adverse event (irAE) from checkpoint inhibitor therapy is consistent with the 2012 European League Against Rheumatism (EULAR)/American College of Rheumatology (ACR) provisional criteria for PMR.

**Methods** The cases were derived from two sources. Group 1 represents reported cases from three contributing centres. Group 2 was derived from a systematic review of the literature searching for all cases reported as PMR or PMR-like illness associated with checkpoint inhibitor therapy. Cases were assessed for the quality of reporting and then analysed to determine whether they fulfilled the 2012 EULAR/ACR provisional criteria for PMR.

**Results** A total of 49 patients were included for analysis. Among the entire group, 37 (75%) were designated 'complete' indicating that they had sufficient data to reliably apply the 2012 EULAR/ACR criteria. 28 (75%) cases fulfilled complete criteria for PMR. A number of cases also demonstrated some clinical features unusual for idiopathic PMR.

**Conclusion** This study suggests a high proportion of reported cases of checkpoint inhibitor-related PMR fulfil preliminary criteria for PMR, yet in one quarter clinical details were incomplete making verification problematic. Furthermore, in the absence of a gold standard for the diagnosis of PMR, the relationship of checkpoint inhibitor-related PMR to the idiopathic form remains unclear.

## Key messages

### What is already known about this subject?

- Polymyalgia rheumatica (PMR) and PMR-like illness have been frequently reported in the form of case reports and small series as immune related adverse events (irAEs) from checkpoint inhibitor therapy (ICI).
- The majority of reports vary in amount of clinical detail and the relationship between the PMR-like entity occurring in the setting of ICI and de novo PMR remains poorly understood.

### What does this study add?

- This study provides the largest cohort of ICI-related PMR events to date; collected from three international centres who are systematically studying such events, as well as from a systematic review of all cases reported in the literature, and analyses their capacity to fulfil preliminary 2012 European League Against Rheumatism/American College of Rheumatology criteria for PMR.

### How might this impact on clinical practice?

- While three out of four cases with complete reporting meet existing classification criteria for PMR, one in four do not and many cases have atypical features. More detailed assessments and reporting of future cases in prospective studies are needed.

## INTRODUCTION

Checkpoint inhibitor therapy has caused a paradigm shift in the field of oncology, producing significant survival benefits in patients with an ever-growing list of malignancies. Their use, however, is attended by a spectrum of immune related adverse events (irAEs), both general and rheumatic, which threaten their overall effectiveness.[1] A critical and presently unanswered question is what proportion of these rheumatic irAEs represent the occurrence of classic rheumatic diseases or, alternatively, represent new clinical variants with potentially different pathogenesis, clinical course and treatment responsiveness. Despite scattered clinical descriptions,[2–4] little is known about the polymyalgia rheumatica (PMR)-like entity that has been described in the setting of checkpoint inhibitor therapy (ICI). In our experience with rheumatic irAEs we have increasingly encountered patients presenting with PMR-like clinical phenotypes. Traditional PMR still remains a poorly understood syndrome of unknown aetiology and without a diagnostic laboratory test. Clinicians generally rely on the

Table 1 Provisional classification criteria for PMR scoring algorithm

| Feature | Points without ultrasound (0–6) | Points with ultrasound (0–8) |
|---|---|---|
| Morning stiffness lasting >45 min | 2 | 2 |
| Hip pain or limited range of motion | 1 | 1 |
| Absence of RF or ACPA | 2 | 2 |
| Absence of other joint involvement | 1 | 1 |
| ≥1 shoulder with subdeltoid bursitis and/or biceps tenosynovitis and/or glenohumeral synovitis and ≥1 hip with synovitis and/or trochanteric bursitis | n/a | 1 |
| Both shoulders with subdeltoid bursitis, biceps tenosynovitis or glenohumeral synovitis | n/a | 1 |

Required to apply algorithm: age ≥50 years, bilateral shoulder aching and abnormal C reactive protein (CRP) and/or erythrocyte sedimentation rate (ESR).
A score ≥4 is categorised as PMR without ultrasound and a score of ≥5 is categorised as PMR if ultrasound findings are included.
ACPA, anti-cyclic citrullinated peptide antibody; PMR, polymyalgia rheumatica; RF, rheumatoid factor.

presence of a compatible clinical picture combined with the detection of inflammatory markers as well as corticosteroid response as a 'test of treatment' to establish the diagnosis. A joint working group from American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) described a provisional set of classification criteria for PMR, incorporating select elements of the history and physical exam combined with select laboratory and imaging findings.[5] It is the purpose of this study to address whether cases of PMR reported as irAEs are consistent with that defined by these current classification criteria. Here, we describe in detail the largest series of patients to date with the PMR-like syndrome in the setting of ICI therapy as well as all previous case reports to determine if they meet the 2012 EULAR/ACR provisional criteria for PMR.

## MATERIALS AND METHODS

Case series: cases from each participating centre (Cleveland Clinic Foundation, Johns Hopkins University, University Hospital of Bordeaux) were prospectively collected from ongoing cohorts extending from February 2015 to present. Data were collected on age, sex, tumour type, checkpoint inhibitor, presence or absence of elevated acute phase reactants, bilateral shoulder aching, morning stiffness >45 min, hip pain, rheumatoid factor (RF)/anti-cyclic citrullinated peptide antibody (ACPA) and presence of other joint involvement (table 1). The diagnoses of PMR were based on expert opinion of the evaluating rheumatologists, and clinical judgement was used to determine whether PMR was attributable to ICI.

A systematic literature search was performed in PubMed and Ovid Embase using the search terms 'polymyalgia rheumatica' (MESH) OR 'polymyalgia rheumatica' AND 'immunotherapy' OR 'checkpoint inhibitor therapy' through 1 April 2018. The equivalent Emtree terms were used in the Embase search.

In 2012, EULAR and ACR published consensus-based classification criteria for PMR.[5] Details of eligibility and the scoring system are included in table 1. A score of ≥4 has 68% sensitivity and 78% specificity for identifying PMR. There are additional points for musculoskeletal ultrasound findings (shoulders or hips), which increase the specificity to 81%, but are not required for classification. We appraised among the reported cases how many provided adequate information to apply the EULAR/ACR criteria for PMR. These were designated as 'complete.' The remainder were designated as 'incomplete.'

## RESULTS

A total of 49 patients were included for analysis: nine cases from Cleveland Clinic, four cases from Johns Hopkins University, seven cases from University Hospital of Bordeaux (table 2) and 29 cases found by systematic review (online supplementary table 3). Of all cases combined, 37 (75%) were designated 'complete.' The remaining 12 (25%) were designated 'incomplete' and thus censored from further evaluation. Of the 20 patients from the three centres, 18 had complete data (90%), compared with 62% from the systematic review. Within the complete group, 28/37 (75%) fulfilled EULAR/ACR criteria for PMR. Eight patients also met imaging criteria. The main reason for failure to meet criteria was the presence of other joint involvement—most commonly knees, followed by hands and elbows. Of patients from the three centres, 9/20 (45%) had involvement of other joints, 6/20 (30%) had normal inflammatory markers and five patients had profound morning stiffness, with explosive onset noted in one individual; within hours of the patient's first ICI infusion with pain and stiffness preventing independent transfer from bed. Two patients had low-positive RF and one had low positive ACPA. One case described a patient with remitting seronegative symmetrical synovitis with pitting oedema. Of 20 patients from our three centres, the median time to onset of PMR symptoms was 12 weeks after start of ICI; tumour was active in 8/20 (40%). In the whole group, the specific ICI was reported in 33/49 (67%) cases: 12 were exposed to nivolumab, five to combination ipilimumab/nivolumab, nine to pembrolizumab, four to ipilimumab, two to

**Table 2** Characteristics of 20 patients from three centres

| Patient | Age/ Sex | Tumour type | Checkpoint inhibitor | Fulfilled EULAR/ACR classification criteria* | Unfulfilled criteria | Atypical features | Treatment |
|---|---|---|---|---|---|---|---|
| Cleveland Clinic Foundation, Cleveland, Ohio, USA | | | | | | | |
| 1 | 63 M | RCC | Nivolumab | No; five points | Acute phase reactants | | Prednisone 40 mg; tocilizumab 162 mg q2 weeks |
| 2 | 69 M | Melanoma | Ipilimumab/ nivolumab | Yes; six points | | Sicca symptoms; antinuclear antibody 1:1280, anti-Sjogren's-syndrome-related antigen A >8 IU | Prednisone 30 mg |
| 3 | 79 M | Melanoma | Ipilimumab/ nivolumab | Yes; seven points† | | Sicca symptoms | Prednisone 20 mg |
| 4 | 57 M | Melanoma | Pembrolizumab | No; three points | Acute phase reactants; RF 35 IU/mL; knee involvement | | Prednisone 60 mg |
| 5 | 60 M | Melanoma | Pembrolizumab | No; three points | RF 45 IU/ mL; knee involvement | | Prednisone 60 mg |
| 6 | 66 M | Melanoma | Nivolumab | Yes; five points | Hand involvement | | Prednisone 20 mg; methotrexate |
| 7 | 69 F | RCC | Nivolumab | Yes; five points | Hand involvement | | Prednisone 10 mg; tocilizumab 162 mg q2 weeks |
| 8 | 66 M | RCC | Durvalumab; tremilimumab | Yes; five points | Hand involvement | | Prednisone 20 mg |
| 9 | 72 F | RCC | Avelumab | Yes; four points | Acute phase reactants; hand and knee involvement | | Prednisone 20 mg |
| Johns Hopkins University, Baltimore, Maryland, USA | | | | | | | |
| 10 | 66 M | Lung adenocarcinoma | Pembrolizumab | No; six points | Shoulder aching | | Prednisone 20 mg |
| 11 | 63 F | Poorly differentiated carcinoma with squamous features | Durvalumab | Yes; six points | | | Prednisone 15 mg; hydroxychloroquine |
| 12 | 59 F | Melanoma | Nivolumab | Yes; six points | | | Prednisone 7.5 mg; bilateral trochanter injections |
| 13 | 76 M | Merkle cell carcinoma | Nivolumab | No; four points | | | |
| Centre Hospitalier Universitaire, Bordeaux, France | | | | | | | |
| 14 | 81 M | Melanoma | Pembrolizumab | No; five points | Acute phase reactants; knee involvement | | Prednisone 10 mg |
| 15 | 74 M | Melanoma | Pembrolizumab | Yes; seven points† | | | Prednisone 15 mg |
| 16 | 59 M | Melanoma | Pembrolizumab | No; seven points†* | Acute phase reactants | | Prednisone 10 mg |
| 17 | 65 F | NSCLC | Nivolumab | No; seven points† | Acute phase reactants | | Prednisone 15 mg |

Continued

Table 2 Continued

| Patient | Age/ Sex | Tumour type | Checkpoint inhibitor | Fulfilled EULAR/ACR classification criteria* | Unfulfilled criteria | Atypical features | Treatment |
|---|---|---|---|---|---|---|---|
| 18 | 63 M | NSCLC | Nivolumab | Yes; six points | | Resolved with NSAIDs alone | NSAIDs |
| 19 | 74 M | RCC | Ipilimumab/ nivolumab | Yes; five points | Hand involvement | | Prednisone 10 mg |
| 20 | 77 F | Melanoma | Pembrolizumab | Yes; six points† | Hip pain | | Prednisone 15 mg |

All patients had complete reporting to allow application of the EULAR/ACR classification criteria.
*A score of four or more is needed for PMR classification without ultrasound, and a score of five or more if ultrasound is included.
†Met ultrasound criteria.
ACR, American College of Rheumatology; EULAR, European League Against Rheumatism; NSAIDs, non-steroidal anti-inflammatory drugs; NSCLC, non-small cell lung cancer;PMR, polymyalgia rheumatica; RCC, renal cell carcinoma.

durvalumab and one to avelumab. The remaining 16 cases were treated with anti-PD-1/L1 therapy.

Among the original group of 49, 46 (94%) received glucocorticoids (GC) as initial treatment for rheumatic irAE. The dose and duration were heterogeneous but the majority of patients responded to GC alone, in doses ranging from prednisone 7.5 mg to 60 mg daily. 17/46 (37%) of patients required more than 20 mg of prednisone daily. Three patients responded to non-steroidal anti-inflammatory drugs alone. Two patients ultimately were treated successfully with tocilizumab 162 mg subcutaneously every other week as a GC-sparing agent. Three other patients required disease modifying anti-rheumatic drugs (methotrexate, hydroxychloroquine).

## DISCUSSION

PMR is increasingly recognised as one of the most common inflammatory rheumatic irAEs, based not only on the volume of clinical reports and clinical series, but also in a recent pharmocovigilance study demonstrating a fivefold elevated risk for developing PMR with ICI therapy versus cancer patients not treated with similar immunotherapies.[6] A reasonable question at present is whether these cases of irAE-PMR represent a disorder identical to the idiopathic form of the disease or rather a new nosologic entity. Answering this is problematic however, given our lack of understanding of its etiopathogenesis and the absence of any highly specific diagnostic test. Given these obstacles, the EULAR/ACR classification criteria provide a logical starting point to address whether ICI-related PMR is similar or different.

Overall our data suggest a mixed picture. In our combined series 25% of reported cases supplied insufficient data to apply the current classification criteria while of the remaining cases with complete reporting, 75% of those met classification criteria but frequently contained atypical features which would suggest that in these cases may represent a different entity. It should be noted that a number of atypical features (synovitis, positive serology for rheumatoid arthritis) were disqualifying. Another atypical feature is a more severe presentations than generally encountered in classical PMR.

Another clinically relevant finding that may also speak to differences in pathogenesis between traditional PMR and ICI-induced PMR is that, 37% of cases required more aggressive therapy with GC than is traditionally used to treat PMR. With regards to the initial GC dose, the heterogeneity and higher initial doses may reflect clinicians' lack of confidence in diagnosis; some patients may have had GCs initiated by their oncologist, prior to referral to rheumatology. Among our multi-centre case series, 20% (4/20) received a GC-sparing agent, with two cases responding well to the IL-6 inhibitor tocilizumab after failing repeated efforts to reduce GC dose to the standards generally utilised in idiopathic PMR. It has been suggested the rheumatic irAEs differ from other system irAEs in that inflammation may persist, even after cessation of checkpoint inhibitor therapy, and require prolonged treatment.[4 7 8] Notably, both patients from our series who required tocilizumab have required it long term, currently 24 months in one patient. In the literature, tocilizumab has been successfully used to treat inflammatory arthritis from ICI as well as irAEs involving other systems, suggesting a pathogenic role of IL-6 and thus Th17 cells in autoimmunity and the development of irAEs.[9 10] Also notable was that seven patients had normal acute phase reactants at the time of PMR diagnosis.

The strengths of the current study include the size of the cohort and collaborative design among three institutions prospectively collecting data on all rheumatic irAEs over the study period. There are, however, several significant limitations, emblematic of many studies published in this early phase of clinical research in the rheumatic irAE era, which deserve mention. The retrospective nature of the current study limits our ability to estimate disease incidence. Case finding may also be potentially confounded by a referral bias, as it is conceivable that some additional patients may have been treated by oncologists without referral to rheumatology and thus may have not been included. In addition, outside of the 20 cases from our own institutions, we are subjected to

limitations of reporting bias for critical elements of the ACR/EULAR criteria which were unavailable in many cases for those identified via our literature search. It is possible that some of these cases could conceivably be reclassified if additional data were available.

A burning question in the field of irAEs is whether diseases which closely resemble de novo autoimmune disease states are actually examples of the classical forms of such disorders or new entities. Based on our study we believe we have identified a meaningful proportion of cases from our multicentre experience and the extant literature that appear to fall outside of what appears to be reasonable in terms of their overall clinical picture suggesting that at least some may represent a new clinical entity. Moving forward our data underscore the urgency for prospective registry-based studies with uniform assessment and reporting of data.

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**Competing interests** CC speaks for Regeneron/Sanofi. LCC received a research grant from Bristol-Myers Squibb and consults for Regeneron/Sanofi. MK consults for Bristol-Myers-Squibb. TB is a fellow supported by T32 grant. EK consults for Celgene, Horizon, Novartis, Regeneron and speaks for Merck and Sanofi. LC consults for Bristol-Myers-Squibb, Genentech and Astra-Zeneca.

**Patient consent for publication** Not required.

**Ethics approval** This study obtained ethics approval through the ethics committees at the Cleveland Clinic (IRB# 17-575), Johns Hopkins University (# CIR00041091) and Centre Hospitalier Universitaire (local ethics committee #CE-GR-2017/007).

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**Data sharing statement** All data relevant to the study are included in the article or uploaded as supplementary information.



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