The Oncologist, 2022, **27**, e353–e356
https://doi.org/10.1093/oncolo/oyac026
Advance access publication 5 March 2022
Brief Communication

Joint-Predominant Rheumatic Complications of Immune Checkpoint Inhibitor Therapy in Patients with Thymic Epithelial Tumors

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Abstract

Immune checkpoint inhibitors (ICIs) have revolutionized the treatment of advanced cancers. However, activation of the immune system can occasionally cause life-threatening toxicity involving critical organs. Induction of immune-mediated toxicity is a significant concern for patients with thymic epithelial tumors (TETs) due to defects in immune tolerance. An increased risk of skeletal and cardiac muscle inflammation following treatment with ICIs is well recognized in patients with advanced TETs. However, uncommon musculoskeletal and rheumatic complications can also occur. The cases presented in this report highlight the spectrum of presentation of immune-mediated, joint-predominant musculoskeletal adverse events in patients with advanced TETs treated with ICIs, including polymyalgia rheumatica-like illness and inflammatory arthritis.

Key words: thymic epithelial tumors; immunotherapy; polymyalgia rheumatica; myositis; inflammatory arthritis.

Introduction

Reinvigoration of antitumor T-cell activity by immune checkpoint inhibitors (ICIs) can cause immune-related adverse events (irAEs), including rheumatic and musculoskeletal complications such as inflammatory arthritis, myositis, and polymyalgia-like illness.[1,2] Patients with thymomas and thymic carcinomas (TCs), collectively referred to as thymic epithelial tumors (TETs), are at high risk for development of irAEs due to underlying defects in immunological tolerance.[3]

Idiopathic polymyalgia rheumatica (PMR) is an inflammatory rheumatic disease affecting adults above 50 years and is characterized by persistent achiness and morning stiffness of the shoulders, neck, and pelvic girdle with elevated inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).[4] The etiologies of both traditional PMR and ICI-induced PMR-like illness are poorly understood.[5]

We describe the clinical and immunological characteristics of ICI-induced, joint-predominant rheumatic irAEs in patients with TETs, including PMR-like syndrome. Patients included in this case series provided informed consent for treatment and were enrolled in one of 2 clinical trials (NCT03076554 and NCT02146170). These trials are approved by the National Institutes of Health Institutional Review Board.

Case 1

A 62-year-old man with recurrent tumor-node-metastasis (TNM) stage IVA, WHO subtype B2 thymoma was enrolled in a clinical trial of avelumab, an anti-PD-L1 antibody (NCT03076554). His course was complicated by pure red cell aplasia which was treated with cyclosporine and prednisone. Three months after discontinuation of immunosuppressives and 26 months after start of avelumab, he developed pain in hip and shoulder joints with morning stiffness lasting over 1 hour. Workup was negative for rheumatoid arthritis

Received: 12 October 2021; Accepted: 10 January 2022.

(RA), myasthenia gravis and myositis, and a clinical diagnosis of PMR was established. Prednisone was started at 10 mg/day and symptoms resolved within hours. Symptoms reappeared when the dose was tapered to 7.5 mg/day and resolved with dose escalation to 10 mg/day. A more gradual taper of 1 mg/day/month was well tolerated with dose reduction to 4 mg/day.

Case 2

A 68-year-old woman with recurrent TNM stage IVA TC was enrolled in the same trial (NCT03076554). After 16 weeks, she developed sicca syndrome that responded to a 6-week course of prednisone 10 mg/day. Twenty months later sicca symptoms returned, accompanied by right-sided chest pain radiating to the right shoulder, generalized weakness, fatigue, and weight loss. The patient denied joint problems, morning stiffness, visual symptoms, or skin rash. Rheumatology evaluation on 10 mg/day of prednisone was inconclusive for PMR or giant cell arteritis. Prednisone dose was increased to 50 mg/day and gradually tapered to a maintenance dose of 5 mg/day within 15 weeks as symptoms improved.

Case 3

A 67-year-old man with recurrent TNM stage IVB TC was treated with pembrolizumab. Six months later he developed adrenal insufficiency and started prednisone 1 mg/kg/day. Upon tapering to 10 mg/day, he developed pain and swelling of the ankles and wrists. He experienced 3 weeks of progressive knee, ankle, wrist, and shoulder pain and stiffness. His rheumatologist recommended increasing prednisone to 40 mg/day, which was effective. However, symptoms returned when the dose was tapered to 10 mg/day, this time with predominant involvement of interphalangeal joints and wrists with limitation in movement suggestive of ICI-related polyarticular inflammatory arthritis. Due to recurrent flares and inability to wean prednisone, methotrexate was initiated (details in Table 1) with improvement of symptoms.

Selected clinical and laboratory information for all patients is presented in Tables 1 and 2.

Immunological Analyses

Patients receiving avelumab had high pre-treatment levels of soluble CD40 ligand (sCD40L), and interleukin (IL)-8 (Supplementary Table S1). Following 2 weeks of treatment, there was an early increase in sCD40L in both cases (13% and 46%). Furthermore, case 1 had high pre-treatment levels of CD4 cells, and low levels of regulatory T cells, natural killer (NK) cells, NK-T cells, and B-cells (Supplementary Table S1).

Discussion

To our knowledge, these are the first prospective data of ICI-induced PMR-like illness in patients with TETs. Two of 3 patients had TC, a disease in which paraneoplastic autoimmunity and ICI-induced irAEs occur less often than in association with thymoma. All patients had an objective anti-tumor response. Reintroduction of the ICI with concurrent low-dose oral corticosteroids was feasible in all cases.

ICI-induced PMR/PMR-like illness occurs in 1%-2% of patients at a median of 12 weeks after initiation of treatment.[2,5] However, symptoms can develop after several months and presentation can be atypical. One in 4 cases do not meet criteria for diagnosis of PMR.[2] Erythrocyte sedimentation rate or CRP may be elevated due to malignancy, making it challenging to use these markers for diagnosis and follow-up. Atypical clinical features make it difficult to distinguish PMR from other rheumatologic complications, such as inflammatory arthritis. Response to steroids can be suboptimal and patients might require treatment with disease-modifying anti-rheumatic drugs or anti-cytokine therapies, including tocilizumab. Corticosteroids, when effective, should be tapered gradually over several months to decrease recurrence risk. Giant cell (temporal) arteritis can occur with ICI-induced PMR and cause visual changes, headaches, temporal pain, and jaw claudication.[2]

Table 1. Clinical features and management of joint-related symptoms, and best response of thymic epithelial tumor to immune checkpoint inhibitor treatment.

	ICI received	Best response of TET to ICI	Interval between ICI initiation and joint symptoms	ICI held	Management of joint symptoms			Other irAE	Autoantibodies
					ICI rechallenge	Immunosuppression	Degree of improvement		
Patient 1	Avelumab	PR	26 months	Yes	Yes	Prednisone	Significant	PRCA	None
Patient 2	Avelumab	PR	24 months	Yes	Yes	Prednisone	Significant	Sjögren's syndrome	RF, ANA, Ro/SSA
Patient 3	Pembrolizumab	PR	9 months	Yes	Yes	Prednisone, Methotrexate[a]	Significant	Hypothyroidism	RF, Anti-CCP, AChR-binding Ab, Proteinase-3

[a]Methotrexate was started at a dose of 10 mg orally daily and increased to 15 mg orally daily after 1 month with a decrease in joint pain. Three months later methotrexate was switched to 20 mg subcutaneous weekly and increased to 25 mg subcutaneous weekly after 6 months with further improvement of symptoms. Patient 3 also received meloxicam 7.5 to 15 mg orally daily for 4 weeks with no response.
Abbreviations: 3ICI, immune checkpoint inhibitor; TET, thymic epithelial tumor; irAE, immune-related adverse event; PR, partial response; PRCA, pure red cell aplasia; RF, rheumatoid factor; ANA, anti-nuclear antibody; Ro/SSA, Sjögren's syndrome-related antigen-A; CCP, cyclic citrullinated peptides; AChR, acetylcholine receptor; Ab, antibody.

Table 2. Results of select laboratory tests and inflammatory markers prior to onset of joint symptoms, at onset of joint symptoms, and upon resolution of symptoms.

Laboratory parameter (reference range)	Prior to onset of joint symptoms	Approximate duration from onset of joint symptoms				
		0	4 weeks	8 weeks	12 weeks	Resolution
Patient 1						
HGB (13.7-17.5), g/dL	12.1	9.8	12.9	12.3	13.3	14.5
HCT(40.1-51.0), %	38.0	32.0	43.0	39.6	42.3	45.7
Platelets (161-347), K/μL	**464**	**441**	**491**	**376**	**375**	318
ESR (0-25.0), mm/hr			12.0	**79.0**	**63.0**	13.0
CRP (0-4.99), mg/L		**106** (0-10)	**5.60**	**138.0**	**86.40**	**30.30**
CK (39-308), U/L	16	21	18	17	20	32
TSH (0.27-4.20), μIU/mL	0.63	4.07	**4.26**	1.64	5.23	2.57
Free T4 (0.9-1.7), ng/dL	**1.9**		1.4	1.2	1.3	1.2
Patient 2						
HGB (11.2-15.7), g/dL	10.6	10.2	9.4	9.9	9.4	8.9
HCT(34.1-44.9), %	33.8	34.0	30.4	33.7	31.4	30.3
Platelets (173-369), K/μL	366	**393**	303	**528**	**433**	**415**
ESR (0-42.0), mm/hr		**67.0**				
CRP (0-4.99) mg/L		**14.20**				
CK (26-192), U/L	50	32	32	37	32	32
TSH (0.27-4.20), μIU/mL	1.54		0.59		1.89	0.65
Free T4 (0.9-1.7), ng/dL	1.0		1.0		1.2	1.3
Patient 3						
HGB (13.0-17.7), g/dL	12.1 (13.7-17.5)	11.1	10.9		10.5	11.7
HCT (37.5-51.0), %	36.2 (40.1-51.0)	34.8	35.9		31.7	34.4
Platelets (150-450), K/μL	261 (161-347)	**555**	375		**472**	365
ESR (0-30), mm/hr			**95**	**40**		**69**
CRP (0-10), mg/L			**106**	**50**		**48**
CK (39-308), U/L	55	20				
TSH (0.28-4.0), μIU/mL	3.23 (0.27-4.20)	**7**	**8**		2.1	
Free T4 (0.9-1.7), ng/dL	1.0					

Laboratory parameters shown above were chosen to confirm that symptoms were not associated with severe anemia (hemoglobin and hematocrit), myositis (creatine kinase), or severe hypothyroidism (thyroid stimulating hormone and free thyroxine). Acute phase reactants and markers of inflammation (platelet count, erythrocyte sedimentation rate, and C-reactive protein) are included to track results in relation to joint symptoms. Abnormally high laboratory results are shown in bold font. Alternate reference ranges are indicated with results.
Abbreviations: HGB, hemoglobin; HCT, hematocrit; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; CK, creatine kinase; TSH, thyroid stimulation hormone; Free T4, free thyroxine.

Patients with TETs receiving ICIs are at risk for developing immune-mediated myositis.[3] Overlapping symptoms, like fatigue, and elevated inflammatory markers make accurate diagnosis challenging. However, in contrast to myositis, which is often characterized by muscle weakness and elevated muscle enzymes, PMR is characterized by muscle pain and morning stiffness.[2]

Pre-treatment evaluation of soluble factors and cytokines in 2 of 3 patients included in this series showed high levels of sCD40L and IL-8 in both cases, including a 2-fold increase in sCD40L and a 200-fold increase in IL-8 in the patient who met clinical criteria for a diagnosis of PMR compared with subjects with TETs treated with avelumab who did not develop any joint-related complications. When CD40 interacts with its ligand (CD154), it initiates several immune events including enhanced antigen presentation and antibody production, generation of memory B-cells and plasma cells, and an increase in cytokine production, including TNF-α, IL-6, and IL-8.[6] Upregulation of CD40 and CD154 and an increase in sCD40L have been described in various autoimmune diseases, including RA.[6-8] Several cytokines are also implicated in the pathogenesis of RA, including IL-8.[9] If validated in a larger cohort of ICI-induced PMR, our finding of elevated sCD40L and IL-8 can provide additional opportunities for therapeutic intervention, especially in steroid-resistant cases.[6,9]

Conclusions

In summary, patients with TETs can experience a spectrum of ICI-induced rheumatic toxicities, including PMR-like illness. Symptoms can arise late, and clinical presentation can be atypical. Corticosteroids should be tapered gradually, and patients should be monitored for symptoms of giant cell arteritis. Further research is required to understand the biology of ICI-induced PMR.

Acknowledgments

The authors gratefully acknowledge the contributions of Ms. Susan Sansone, patient care coordinator, Thoracic and GI Malignancies Branch, NCI, toward scheduling clinic and laboratory appointments for individuals included in this case series. The authors thank Ms. Debra Weingarten from the Office of the Chief, Laboratory of Tumor Immunology and Biology, NCI, and Ms. Gisela Butera from the NIH Library, Office of Research Services, U.S. Department of Health and Human Services, Bethesda, MD, for editorial assistance in the preparation of this manuscript.

Funding

This research was supported in part by the Intramural Research Programs of the National Institutes of Health National Institute of Arthritis, and Musculoskeletal and Skin Diseases and the National Cancer Institute (NCI), Center for Cancer Research, and through a Cooperative Research and Development Agreement between the NCI and EMD Serono, Billerica, MA, USA.

Conflict of Interest

The healthcare business of Merck KGaA, Darmstadt, Germany, and Pfizer reviewed the manuscript for medical accuracy only before journal submission. The authors are fully responsible for the content of this manuscript, and the views and opinions described in the publication reflect solely those of the authors. The authors indicated no financial relationships.

Author Contributions

Conception/design: C.M., A.R. Provision of study material/patients: C.M., H.C., S.S., M.M., T.P., S.G., P.J.L., A.R. Collection and/or assembly of data: C.M., M.B., S.S., M.M., Y.-T.T., R.D., T.P., S.G., J.S., J.G., A.R. Data analysis and interpretation: H.C., Y.-T.T., R.D., S.G., P.J.L., J.S., J.G., A.R. Manuscript writing: C.M., M.B., R.D., S.G., J.S., J.G., A.R. Final approval of manuscript: All authors

Data Availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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