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Research Letter

Arthroplasty Joint Histology and Surgical Outcomes in Patients on Immune Checkpoint Inhibitors: A Single-Center Case Series

PLAIN LANGUAGE SUMMARY.
This is a case series of 16 patients with cancer who were treated with immune checkpoint inhibitor (ICI) therapy and who underwent 23 joint replacements. Some of these patients were known to have inflammatory arthritis (joint inflammation) as a side effect of the ICI therapy, whereas others were thought to have worsening of established osteoarthritis (OA). We wanted to know whether the patients with OA had ICI-related joint inflammation that was simply not recognized before surgery. We also wanted to know whether patients who undergo joint replacements on ICI have more surgery complications than other people. What we found was that the people who were diagnosed with OA prior to surgery had OA on joint histology. Only the patients with known inflammatory arthritis from ICI had significant inflammation on joint histology. One patient required a revision of her hip joint replacement 3.7 years after surgery (while still on ICI) due to an inflammatory reaction to her joint replacement. We could not determine whether ICI played a role in that complication.

To the Editor:

Immune checkpoint inhibitors (ICIs) have transformed cancer treatment but can cause immune-related adverse events (irAEs) including inflammatory arthritis (ICI-IA).[1] ICI-IA occurs in 4% of patients treated with ICI[2] and can resemble rheumatoid arthritis (RA) histologically, with hyperplastic synovium and dense lymphoplasmacytic infiltrates.[3] Some investigators have suggested that a preexisting diagnosis of osteoarthritis (OA) is associated with an increased risk of ICI-IA.[4] Cancer patients with preexisting OA may present to an orthopedist or rheumatologist with worsened OA pain during ICI treatment, and may even require an arthroplasty. This has been termed "activated OA,"[5] but whether it actually represents an irAE has not been determined histologically.

Whether ICI increases the risk of arthroplasty complications, such as early revision, infection, dislocation, venous thromboembolism, myocardial infarction, stroke, or death, is also unknown.[6] Patients with RA are at a higher risk for complications, especially infection and revision, than patients with OA[7]; this increased risk is potentially due to immunomodulatory therapy, or the inflammatory process itself, which could also be relevant to ICI-treated patients.

In this study, we assessed joint histology and surgical outcomes of ICI-treated cancer patients who underwent arthroplasty at a single center between January 1, 2018, and August 2, 2023. Joint explant histology was reviewed, and clinical data were extracted from the electronic health record through September 30, 2023.

We identified 16 ICI-treated patients with a variety of cancers who underwent 23 arthroplasties (Table). The mean (SD) age was 68 (10) years, BMI (calculated as weight in kilograms divided by height in meters squared [kg/m^2]) was 28.1 (3.7), and median (IQR) Charlson comorbidity index 8.0 (4.0-8.5). Median (IQR) duration of ICI was 19.0 (7.0-30.5) months and time from last dose of ICI to first arthroplasty was 126.0 (18.5-362.5) days. Seventeen out of 23 (74%) surgeries were performed within 1 year of last ICI. Median (IQR) duration of follow-up after the first surgery was 346 (100-587) days.

Five patients (9 arthroplasties) were diagnosed with ICI-IA by a rheumatologist prior to arthroplasty and 3/5 were on immunomodulator therapy at the time of surgery. Joint histology in 6/9 demonstrated chronic proliferative and exudative synovitis with lymphoplasmacytic inflammation, described in some instances as consistent with RA. Patient 2 (Figures 1A,B), as previously reported,[8] had mononuclear cell infiltrates in her first knee; the second knee, replaced 6 months later, had changes indistinguishable from RA, with lymphocyte aggregates and Russell bodies. Patient 14, who had marginal zone lymphoma, developed ICI-IA of his hands, but his hip pain was thought to be due to OA. Histology showed degenerative changes with lymphomatous involvement of the synovium (Figures 1C,D).

The remaining 11 ICI-treated patients had OA without any clinical history of ICI-IA. These patients underwent 14 arthroplasties (11 within 1 year of last ICI); 9 joints demonstrated synovial hyperplasia and sclerosis consistent with degenerative pathology, including 3 joints with calcium pyrophosphate deposition, and 1 joint with secondary osteonecrosis. Five joints had moderate synovial inflammation or lymphoplasmacytic synovitis, which was considered by the pathologist to be within the spectrum of OA.

Patient 1, who underwent total hip arthroplasty while on ICI, presented with recurrent hip pain 44 months after surgery. Magnetic resonance imaging showed synovial expansion and nonspecific pericapsular and extracapsular edema suggestive of an inflammatory process. Her dual mobility prosthesis had a modular dual mobility liner containing cobalt/chromium, and serum cobalt level was elevated at 2.7 μg/L (normal range 0.1-0.4 μg/L). She underwent a hip revision, and histology showed an immune-mediated inflammatory granulomatous

Table. Patient characteristics.

Patient	Age/Sex, IA or OA	Charlson Comorbidity Index/BMI (kg/m²)	Cancer/Stage, RECIST Status	ICI, Duration (months)	Immuno-suppression, mg	Time From Last Dose to Surgery, days	Joint	Length of Hospital Stay, days	Follow-Up After Surgery, days	Histology[a]
Patients diagnosed with ICI-IA by a rheumatologist prior to arthroplasty										
2	72/F IA	9/28.3	Melanoma/IV, CR	Nivolumab, 41	Prednisone 10 MTX 7.5	242	Left knee	3	346	**Chronic proliferative and exudative synovitis with lymphoplasmacytic inflammation, marked, consistent with secondary inflammatory arthritis**
					Prednisone 10 MTX 7.5	365	Right knee	2	223	**Chronic proliferative and exudative synovitis with lymphoplasmacytic inflammation, marked, consistent with rheumatoid arthritis**
					Prednisone 10 MTX 7.5	464	Left hip	3	124	Degenerative joint disease with lymphoplasmacytic synovitis
8	69/M IA	8/29.0	Urothelial/IV, PD	Nivolumab, 84	None	7	Right knee	2	492	**Chronic proliferative synovitis with lymphoplasmacytic inflammation, marked, consistent with rheumatoid arthritis**
13	46/F IA	1/33.7	Melanoma/IV, CR	Ipilimumab + Nivolumab → Pembrolizumab, 9	Prednisone 5	1570	Left knee	2	1085	Degenerative joint disease
					Hydrocortisone 15 QAM / 10 QPM	2267	Right knee	3	388	**Chronic proliferative synovitis with lymphoplasmacytic inflammation, marked, consistent with rheumatoid arthritis**
14	65/M IA	4/28.2	Marginal zone lymphoma, PD	Pembrolizumab, 5	None	275	Right hip	1	47	Degenerative joint disease with findings consistent with involvement by low grade B cell lymphoma
16	69/F IA	8/32.6	Endometrial, NED	Pembrolizumab, 19	Prednisone 5	23	Left knee	1	138	**Chronic proliferative and exudative synovitis with lymphoplasmacytic inflammation**
					Prednisone 7.5 MTX 125	8	Right knee	2	41	**Chronic proliferative and exudative synovitis with lymphoplasmacytic inflammation**
Patients with OA without any clinical history of ICI-IA										
1	67/F OA	8/23.3	NSCLC/IV, PD	Nivolumab, 55	None	5	Right hip	2	1458	Degenerative joint disease, with chronic synovitis
						2	Left hip	3	855	Degenerative joint disease
						11	Right hip revision	3	31	**Inflammatory granulomatous implant reaction**
3	79/F OA	3/23.8	HL, NED	Nivolumab, 5	None	614	Right shoulder	1	350	Degenerative joint disease, with lymphoplasmacytic synovitis, moderate
4	79/M OA	6/25.9	Melanoma/IIC, NED	Nivolumab, 10	None	27	Right hip	1	979	Superficial subchondral subarticular fracture, hip, with secondary osteonecrosis and secondary degenerative joint disease
					None	305	Right knee	2	666	Degenerative joint disease, with moderate synovial Inflammation

Table. Continued.

Patient	Age/Sex, IA or OA	Charlson Comorbidity Index/BMI (kg/m²)	Cancer/Stage, RECIST Status	ICI, Duration (months)	Immuno-suppression, mg	Time From Last Dose to Surgery, days	Joint	Length of Hospital Stay, days	Follow-Up After Surgery, days	Histology[a]
5	87/M OA	10/25.1	Melanoma/IV, CR	Ipilimumab + Nivolumab, 33	None	14	Left hip	4	121	Degenerative joint disease
6	68/M OA	8/30.0	Melanoma/IV, CR	Niovlumab, 19	None	4	Right knee	2	65	Degenerative joint disease
7	67/F OA	8/20.3	Urothelial/IV, CR	Pembrolizum-ab, 27	None	142	Right hip	1	39	Degenerative joint disease, with lymphoplasmacytic synovitis, moderate
9	66/M OA	4/29.0	RCC, NED	Ipilimumab + Nivolumab, 5	None	50	Right knee	1	587	Degenerative joint disease
					None	267	Left knee	1	370	Degenerative joint disease
10	54/M OA	7/28.7	Esophageal/IV, SD	Pembrolizum-ab, 15	None	27	Right knee UKR	1	100	Degenerative joint disease
11	75/M OA	11/29.7	Melanoma/IV, CR	Nivolumab, 28	None	370	Left knee	3	68	Degenerative joint disease, with CPPD
12	48/F OA	1/28.0	Melanoma/IV, CR	Ipilimumab + Nivolumab, 2	None	2278	Right hip	1	446	Degenerative joint disease, with lymphoplasmacytic synovitis, moderate, with CPPD
15	73/M OA	10/35.0	Prostate/IV, CR	Durvalumab, 23	None	355	Right knee	1	239	Degenerative joint disease, with CPPD

[a] Entries in bold have histology demonstrating significant inflammation CPPD: calcium pyrophosphate deposition; CR: complete response; HL: Hodgkin lymphoma; ICI: immune checkpoint inhibitor; IA: preoperative diagnosis of ICI-related inflammatory arthritis; MTX: methotrexate; NED: no evidence of disease; NSCLC: nonsmall cell lung cancer; OA: preoperative diagnosis of osteoarthritis; PD: progressive disease; PR: partial response; RCC: renal cell cancer; RECIST: Response Evaluation Criteria in Solid Tumors; SD: stable disease; UKR: unicompartmental knee replacement.

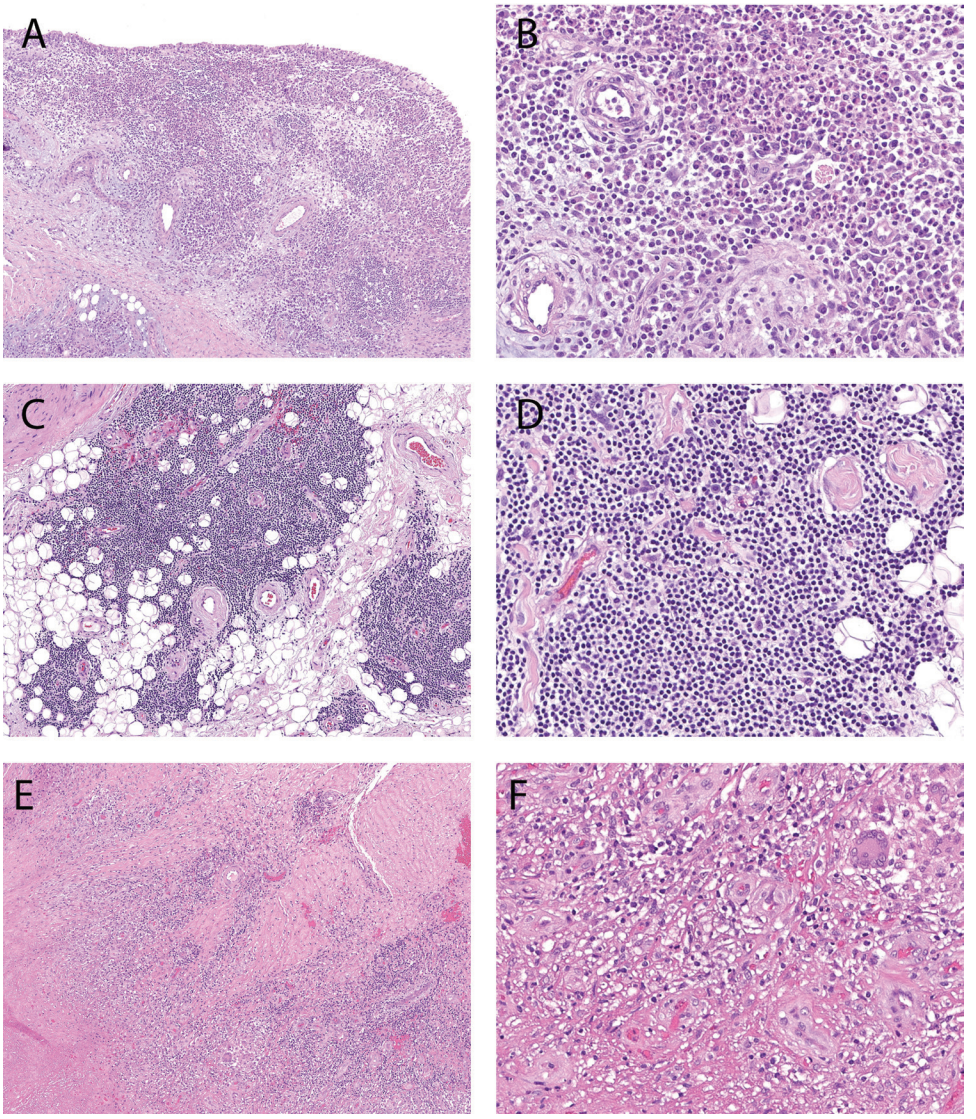

Figure 1. Histology. (A-B) Marked lymphoplasmacytic synovitis (5× and 20×). (C-D) Lymphomatous involvement of synovium (5× and 20×). (E-F) Granulomatous immune reaction with giant cell in (F) (5× and 20×).

reaction (adverse local tissue reaction), possibly from corrosion at the dual mobility liner or from neck/stem metal incompatibility (Figures 1E,F).

There were no surgical site infections, wound healing issues, readmissions, emergency room visits, thromboembolic events, cardiovascular complications, or death within 90 days.

In summary, we previously described a syndrome of activated OA in a subset of ICI-treated patients in whom joints with known OA become more symptomatic without clinical signs of inflammation.[6] In the present study, joint explant histology from patients with activated OA demonstrated nonspecific synovial hyperplasia and sclerosis. Although one-third had a degree of lymphoplasmacytic synovitis, this finding is common in OA in the general population.[9] Our study suggests that ICI-treated patients with an exacerbation of OA pain without other signs of ICI-IA have OA histologically, and not an irAE, whereas patients diagnosed with ICI-IA prior to arthroplasty can have significant synovitis.

Our study demonstrated no short-term complications of arthroplasty in ICI-treated patients with either ICI-IA or OA; however, 1 patient on long-term ICI therapy required revision hip arthroplasty 3.7 years after her initial surgery because of an immune-mediated inflammatory reaction, possibly to her cobalt-containing prosthesis liner.[10] We can only speculate whether this was related to her ICI therapy.

Finally, the synovial findings in the patients with ICI-IA in this study demonstrated a dense lymphoplasmacytic synovitis similar to RA. However other studies have demonstrated B cell–poor synovial histology in some ICI-IA cases.[8] This suggests that ICI-IA may be a heterogeneous condition and/or one that evolves over time.

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COMPETING INTERESTS

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ETHICS AND PATIENT CONSENT

The study was approved by the HSS Institutional Review Board (IRB #2017-1898; IRB #2020-2572; #2014-233-CR11) and all patients signed informed consent.

REFERENCES

1. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med 2018;378:158-68.
2. Kostine M, Rouxel L, Barnetche T, et al. Rheumatic disorders associated with immune checkpoint inhibitors in patients with cancer—Clinical aspects and relationship with tumour response: A single-centre prospective cohort study. Ann Rheum Dis 2018;77:393-8.
3. Murray K, Floudas A, Murray C, et al. First use of tofacitinib to treat an immune checkpoint inhibitor-induced arthritis. BMJ Case Rep 2021;14:e238851.
4. Paiola M, Portnoy DM, Hao LY, et al. Osteoarthritis increases the risk of inflammatory arthritis due to immune checkpoint inhibitors associated with tissue-resident memory T cells. J Immunother Cancer 2025;13:e010758.
5. Reid P, Liew DFL, Akruwala R, Bass AR, Chan KK. Activated osteoarthritis following immune checkpoint inhibitor treatment: an observational study. J Immunother Cancer 2021;9:e003260.
6. Heo SM, Harris I, Naylor J, Lewin AM. Complications to 6 months following total hip or knee arthroplasty: observations from an Australian clinical outcomes registry. BMC Musculoskelet Disord 2020;21:602.
7. Ravi B, Escott B, Shah PS, et al. A systematic review and meta-analysis comparing complications following total joint arthroplasty for rheumatoid arthritis versus for osteoarthritis. Arthritis Rheum 2012;64:3839-49.
8. Wang R, Singaraju A, Marks KE, et al. Clonally expanded CD38hi cytotoxic CD8 T cells define the T cell infiltrate in checkpoint inhibitor-associated arthritis. Sci Immunol 2023;8:eadd1591.
9. Pearle AD, Scanzello CR, George S, et al. Elevated high-sensitivity C-reactive protein levels are associated with local inflammatory findings in patients with osteoarthritis. Osteoarthritis Cartil 2007;15:516-23.
10. Gkiatas I, Sharma AK, Greenberg A, Duncan ST, Chalmers BP, Sculco PK. Serum metal ion levels in modular dual mobility acetabular components: A systematic review. J Orthop 2020; 21:432-7.