Synovial biopsy in a case of nivolumab-induced arthritis

Sirs,

Immune checkpoint inhibitors (ICIs) are valuable therapeutic weapons against cancer that potentiate a T cell-mediated immune response. Nivolumab is an ICI that targets the PD-1 receptor. Rheumatic immune-related adverse events (irAEs), which are induced by ICIs, occur in 10% of cases (1). However, their pathogenesis remains unclear. Synovial biopsy has allowed for a better understanding of the underlying mechanisms of different arthropathies (2).

A 78-year-old man presented in September 2023 with a one-month history of left wrist arthritis. He had stage IV melanoma, diagnosed at age 76, with lymph node and hepatic metastasis, and started nivolumab and ipilumab in April 2023. Due to immune-mediated colitis, this therapy was discontinued in May, and nivolumab was restarted as monotherapy in June. At the first rheumatological evaluation, the patient had left wrist arthritis, raised acute phase reactants (leukocytes 11,500/μL, C-reactive protein 7.45 mg/dL), and mild to moderate synovitis of the radiocarpal, intercarpal, and distal radioulnar joints on ultrasound. Rheumatoid factor, cyclic citrullinated peptide antibodies, and antinuclear antibodies were negative. Considering the possibility of a crystal-induced arthritis, colchicine 1 mg/day and prednisolone 5 mg/day were started.

After 3 weeks without improvement, an ultrasound-guided needle synovial membrane biopsy of the radiocarpal joint was performed. Cultural exams were negative. Histological examination showed a hypertrophic lining with 4–5 layers of synoviocytes, areas of loss of integrity, stromal hypercellularity with moderate lymphoplasmacytic infiltration, and perivascular edema. No crystals were observed. Immunohistochemistry revealed that the infiltrate was rich in histiocytes and CD3+ T lymphocytes, with a mixed population of CD4+ and CD8+ cells. Four CD20+ B cell lymphoid aggregates, with accompanying CD138+ plasma cell proliferation, were identified. PD-1 expression was mild, and PD-L1 staining was weak (Fig. 1). The Krenn score was 6, which is consistent with high-grade synovitis. A diagnosis of nivolumab-related arthritis was made.

In November, the patient presented with bilateral wrist arthritis. Following multidisciplinary discussions, it was decided to continue nivolumab, perform corticosteroid injections of the radiocarpal joints, increase prednisolone dose to 7.5 mg/day, and start hydroxychloroquine 400 mg/day. Subsequently, prednisolone was reduced and discontinued in February 2024, but bilateral wrist arthritis recurred in June, and the patient was retreated with intra-articular corticosteroid injections. Due to progression of the oncologic disease, nivolumab was discontinued in September, and the patient died in April 2025, having experienced no further episodes of arthritis.

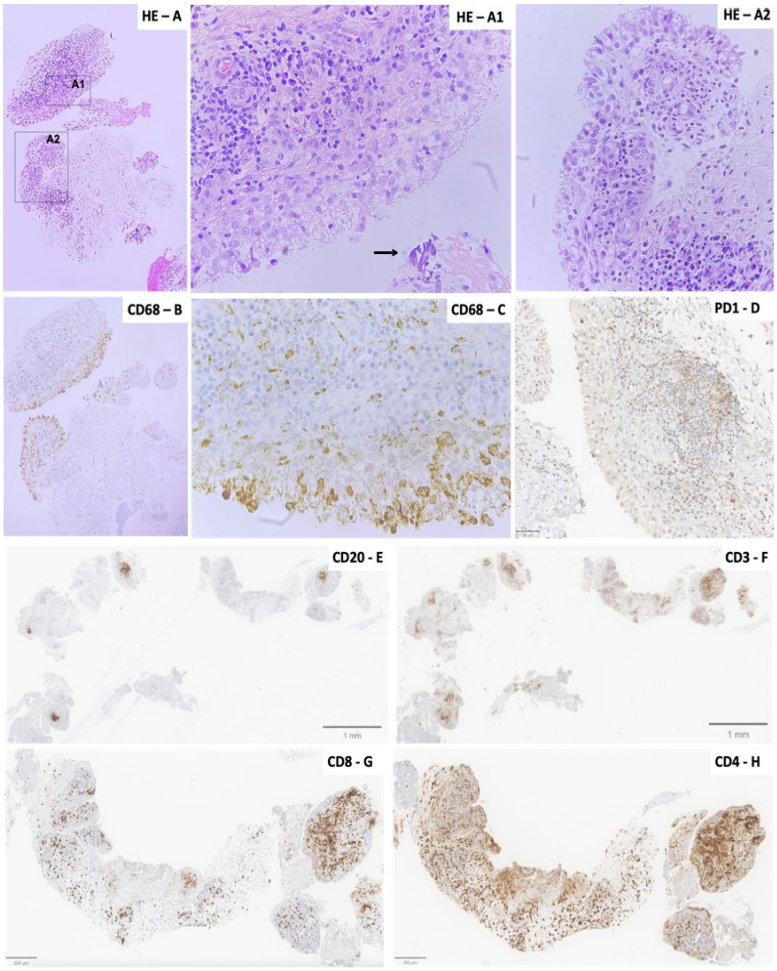

Fig. 1. Histological high grade synovitis: (**A**) a low magnification with 3 fragments of synovial membrane; (**A1** and **A2**) lining layer hyperplasia with 4-5 layers of synoviocytes, mild inflammatory infiltrate and stroma activation; (**A1**) small bone fragments can be seen (arrow). (**B** and **C**) low and high magnification of CD68 staining highlighting the histiocytic phenotype of the synoviocytes in this sample. (**D**) PD-1 diffuse mild staining. (**E**) CD20 staining demonstrating 4 lymphoid aggregates. (**F**) Diffuse CD3 staining. (**G** and **H**) Staining of CD8 and CD4 displays predominance of CD4+ cells.

Previous reports of synovial biopsies from patients with ICI-induced arthritis have shown varying histological features, resembling the diverse phenotypes of rheumatoid arthritis synovium (2). Medina *et al*. reported an oligoarthritis in a nivolumab-treated melanoma patient. Synovial biopsy revealed a chronic lymphoplasmacytic synovitis, with an even mix of T lymphocytes (slight CD4+ predominance) and clustered B cells (3). Murray-Brown *et al*. described a nivolumab-related polyarthritis in a squamous cell carcinoma patient. Synovial biopsy revealed a predominance of lymphoid-organised T cells and macrophages. This patient was refractory to glucocorticoids, hydroxychloroquine, and methotrexate. High TNF levels on immunohistochemistry informed the decision to start infliximab, with a good response (4). Nakayama *et al*. described a nivolumab-induced polyarthritis in a patient with a prior history of rheumatoid arthritis. Synovial biopsy showed a linear inflammatory infiltrate with a predominance of macrophages and CD8+ T cells (5). Our findings, particularly the prevalence of histiocytes and T lymphocytes with sparse B cell clusters, mirror some of the previous descriptions and underscore the diversity of histological presentations.

This case highlights the potential role of synovial biopsy in uncovering the mechanisms underlying irAEs, thus advancing our understanding of these disorders.

Key message

Synovial biopsy has a role in understanding the aetiopathogenesis of immune checkpoint inhibitor-induced arthritis.

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