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HISTOPATHOLOGY OF CHECKPOINT INHIBITORS INDUCED ARTHRITIS: RETROSPECTIVE ANALYSIS OF 3 CASES

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Background: Induced arthritis (IA) is a rare immune related adverse event occurring in 0.5 to 2% of patients exposed to Immune (irAEs) Checkpoint Inhibitors (CPI). In some patients, this condition may be severe and long lasting even after CPI cessation. Cross-reactivity between tumor- and self-antigens was considered in the etiology of several cases of irAEs but disease mechanisms in IA remain elusive.

We systematically collect synovial tissue of patients with IA (Ethical Committee B403201942386).

Objectives: Here, we report the histopathological findings from ultrasound guided (USG) synovial biopsies from the 3 first patients of our cohort. The immune cell infiltration in CPI IA patients is compared to the histopathological findings in rheumatoid arthritis.

Methods: Patients were referred through their oncologist after the onset of an arthritis in the context of a CPI therapy. The diagnostic of arthritis was confirmed by a rheumatologist and by ultrasound assessment. USG biopsies were performed before initiation of specific therapies.

Pathological and immunohistochemical analyses include semi quantitative scoring of the following: synovial hyperplasia, fibrinoid necrosis, chorion cellular infiltrate, vascular hyperplasia, CD3-, CD20-, CD68- and CD138-positive cells.

All patients gave written informed consent.

Results: Three patients went through the USG biopsy procedure: 2 males and 1 female. No adverse events were recorded.

All patients had metastatic neoplasms and time-to-arthritis was on average 6.7 months after CPI initiation. The USG biopsies were performed from 1 week after the onset of the IA to 16 months. The target joints displayed strong synovial thickening on ultrasound. Histological and immunohistochemistry studies showed light to moderate synovial hyperplasia and inflammatory cell infiltration of the sublining by macrophages and T cells, but no or little B cells (Table 1).

Table 1. Clinical Characteristics and histopathological analyses on synovial biopsies.

	Patient 1	Patient 2	Patient 3
Cancer	uterus	bladder	lungs
Biopsied joint	first metatarsophalangeal joint	wrist	knee
Time-to-synovial biopsy	1 week	2 months	16 months
Grey scale on ultrasound	3/3	3/3	3/3
Hematoxylin-eosin staining:			
synovial hyperplasia	+	+	++
fibrinoid necrosis	0	+	++
chorion cellular infiltrate	+	++	+
vascular hyperplasia	0	0/+	++
Immunohistochemistry staining:			
CD3	+	++	+
CD20	0	0	0/+
CD68	++	0/+	++
CD138	0	0	0/+

Conclusion: USG synovial biopsies have been safely performed and the histopathological analysis have confirmed the synovitis with mainly a macrophage infiltrate (myeloid pattern). IA synovitis is characterized by synovial hyperplasia and macrophage and T cell infiltration of the sublining. Increased collaboration between oncologists and rheumatologists is needed to create opportunities for referral of patients between the two specialties and optimize treatment. Further analyses (such as global or single-cell RNA sequencing) are needed to learn more about IA pathophysiology.

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THE CHARACTERISTICS OF PERIPHERAL LYMPHOCYTE SUBSETS IN PATIENTS WITH IGG4-RELATED DISEASE

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Background: Immunoglobulin G4-related disease (IgG4-RD) is an autoimmune disease with chronic systemic inflammation and fibrosis. The main feature of the disease was diffuse swell of the affected organs, and the serum IgG4 level was increased. Histopathology of the lesions showed infiltration of IgG4+ plasma cells. However, the pathogenesis of IgG4-RD is still unclear^[1].

Objectives: To explore the clinical characteristic of lymphocyte subsets of IgG4-related disease patients, and make comparisons with healthy controls.

Methods: A total of 31 patients with IgG4-RD who were admitted to the Rheumatic Immunology Department of the Second Hospital of Shanxi Medical University from January 2016 to June 2020 were included. We collected their clinical and laboratory data, and selected 30 age and sex matched healthy people as the control group. Flow cytometry was used to detect the percentage and absolute number of lymphocyte subsets (T, B, NK, CD4+T, CD8+T) and CD4+T subsets (Th1, Th2, Th17, CD4+CD25+Foxp3+Treg) in peripheral blood of IgG4-RD patients and healthy controls.

Results: (1)The percentage of CD4+T cells in peripheral blood of IgG4-RD patients was higher than that of healthy controls [45.00(33.97-51.48) vs. 39.36(33.78-43.30), P<0.05]. (2)The percentage and absolute number of Th17 cells was increased in IgG4-RD patients [1.13(0.70-1.55) vs. 0.77(0.43-1.07), P<0.05; 7.90(5.20-12.23) vs. 5.60(3.12-8.47), P<0.05], while the percentage of Treg cells was decreased [3.37(2.82-5.65) vs. 4.96(4.18-6.34), P<0.01]. But Treg cells number showed no difference between the two groups. (3) Th17/Treg ratio was significantly increased in IgG4-RD patients [0.29(0.16-0.46) vs. 0.15(0.08-0.23), P<0.01], and it was positively correlated with IgG4-RD response index score(r=0.491, P<0.01). (Table 1).

Table 1. Comparison of absolute number and percentage of peripheral blood lymphocyte subsets between IgG4-RD patients(n=31) and healthy controls (n=30).

cell subsets	IgG4-RD (n=31)	HC(n=30)	P value
B	150.59(120.14-212.38)	203.27(152.90-244.27)	0.089
B%	8.74(6.46-11.45)	10.03(8.26-13.21)	0.059
NK	261.98(178.82-303.08)	290.83(179.93-451.45)	0.175
NK%	13.14(9.92-18.10)	16.50(11.24-21.75)	0.105
CD3+T	1357.44(992.00-1844.82)	1305.81(978.24-1597.94)	0.708
CD3+T%	72.62(69.32-76.96)	71.62(64.97-75.25)	0.135
CD8+T	436.40(342.71-596.86)	513.50(359.73-620.53)	0.665
CD8+T%	24.26(19.48-31.27)	26.50(20.67-32.90)	0.535
CD4+T	741.00(562.78-1095.52)	664.50(585.52-789.97)	0.428
CD4+T%	45.00(33.97-51.48)	39.36(33.78-43.30)	0.032
Th1	162.32(108.11-216.61)	144.27(81.52-161.66)	0.094
Th1%	19.00(15.24-25.54)	18.46(14.86-24.27)	0.644
Th2	7.82(5.35-11.78)	8.25(5.32-10.87)	0.817
Th2%	1.00(0.76-1.27)	1.24(0.89-1.64)	0.399
Th17	7.90(5.20-12.23)	5.60(3.12-8.47)	0.010
Th17%	1.13(0.70-1.55)	0.77(0.43-1.07)	0.026
Treg	24.45(19.76-44.79)	34.55(27.29-46.57)	0.076
Treg%	3.37(2.82-5.65)	4.96(4.18-6.34)	0.003
Th1/Th2	20.00(13.78-36.36)	14.97(10.31-21.58)	0.135
Th1/Treg	5.72(2.92-8.86)	3.68(2.53-4.77)	0.021
Th2/Treg	0.27(0.16-0.52)	0.22(0.15-0.32)	0.199
Th17/Treg	0.29(0.16-0.46)	0.15(0.08-0.23)	0.002

Conclusion: Th17/Treg immune disorder exists in IgG4-RD patients, and it is related to the disease activity, indicating that Th17/Treg imbalance may be an important pathogenesis of IgG4-RD.

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IGG4-RELATED CORONARY PERIARTERITIS: SYSTEMATIC LITERATURE REVIEW WITH OUR CASE SERIES

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