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JOINT MANIFESTATIONS SECONDARY TO IMMUNOTHERAPY: CLINICAL CHARACTERISTICS AND EVOLUTION

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Background: Inhibitors of CTLA-4 and PD-1 have shown improvements in survival in multiple advanced cancers. Immune-mediated effects such as arthralgias and arthritis have been described, but their prevalence and characteristics have not been well defined.

Objectives: The objective of the study is to describe the prevalence of immunomediated joint manifestations (IJM), its characteristics and evolution in patients who received immunotherapy (nivolumab (NV), pembrolizumab (PB)) from January 1, 2016 to December 31, 2018 in our center.

Methods: Data collection was performed at through the RPT (Registre Pacients Tractats) database of the CatSalut, and the patients referred to the monographic medical office of inflammatory joint diseases of our center. In all cases, the variables: age, sex, neoplasia, drug, number of doses, were recorded. In patients with joint involvement: other autoimmune manifestations, joint affection prior to treatment, delay rheumatology derivation, joint affection type, swollen and tender joint counts, ESR, CRP, RF, ACPA, ANA, HLA B 27, Hb, leukocytes, neutrophils, lymphocytes, treatment and evolution, were recorded. The statistical analysis was carried out with the SPSS 15.0 computer package

Results: 106 patients received treatment (TTO) with immunotherapy (71 NV, 35 PB) for neoplasia (81 lung, 10 renal, 8 melanoma, 2 oropharynx). The mean age was 67.93 ± 10.7 years (21.7% women, 78.3% men). There were 11 events cataloged as IJM. The overall prevalence was 10.3% (5.6% NV, 14.3% PB). Patients with IJM received a greater number of doses (17.67 ± 9.3 vs 9.24 ± 10.1 p = 0.018). No patient with melanoma presented IJM. All IJM suspicions cases were assessed by a rheumatology. When studying their characteristics (Table 1), 3 patients were added from the database of the rheumatology service (14 cases). They received in a clinical trial BP29541 (rectal cancer), Atezolizumab (lung cancer) and Durvalumab (lung cancer). 42.9% of the patients presented inflammatory arthralgias (IAT) and 57.1% arthritis (AT). In reference to their previous history, 2 patients had a history of hyperuricemia and arthritis. One patient concomitantly presented lymphocytic colitis confirmed by biopsy. The delay time for assessment by rheumatology was 18.1 ± 22.1 days. Patients with AT were older (p = 0.014), had higher ESR (p = 0.047) than those with IAT. No differences were found in other variables (table1). With reference to the analytical study, 1 patient was RF +, 2 ANA + at mean titers (1/160-1/320), none ACPA or HLA B 27 +. After assessment by rheumatology, two patients with IAT were diagnosed with bone M1 and two AT were categorized as gouty arthritis. The rest of the IAT responded to NSAIDs, did not require corticosteroids and were resolved. 6 cases of AT received prednisone, 3 required treatment dose 1 mg/kg weight and subsequently MTX in 2 of them, with evolution to low disease activity at present. Only one patient met RA classification criteria.

Conclusion: The prevalence of IJM was higher than 10%, depending on the number of doses. Patients with arthritis had higher age and higher ESR. No patient presented ACPA and HLA B 27 +, so to include them in the initial analytical could be not necessary. In these patients, it is important the assessment by a rheumatologist to make a correct differential diagnosis, as well as establish referral circuits to avoid delay of care

	ARTHRITIS (AT)	ARTHRALGIA (IAT)	P value
Age	71 ± 6,0	59,3 ± 9,7	0,014
Swollen joints	3,63 ± 3,4	0	0,026
Painful joints	10,75 ± 15,7	10,0 ± 8,7	0,919
ESR	39,5 ± 25,3	9,0 ± 4,3	0,047
CRP (mg/dl)	15,6 ± 11,6	5,0 ± 8,8	0,156
Leukocytes (cel x 10 ³)	11,026,2 ± 3264,2	8,156 ± 3,357,6	0,134
Lymphocytes (cel x 10 ³)	1,696,2 ± 1042,8	1,836,6 ± 1,188,4	0,818
Neutrofilos (cel x 10 ³)	8263,7 ± 2,668	5,523,6 ± 3,531	0,123
Hb(mg/dl)	10,8 ± 2,1	12,1 ± 2,64	0,325

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BIOLOGICAL THERAPY IN NON ISCHAEMIC OPTIC NEURITIS ASSOCIATED TO IMMUNE-MEDIATED INFLAMMATORY DISEASES. MULTICENTER STUDY

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Background: Non ischaemic optic neuritis (NION) is a severe inflammation of the optic nerve that may lead to blindness. It can be primary or associated to immune mediated inflammatory diseases (IMIDs). The treatment of the NION is based on systemic corticosteroids and conventional immunosuppressive drugs.

Objectives: To assess the efficacy of the biological treatment in refractory NION to conventional treatment.

Methods: Multicenter study of 12 patients diagnosed with NION refractory to systemic corticosteroids and at least one conventional immunosuppressive drug. The main outcomes were visual acuity (VA) and optical coherence tomography (OCT) of the optic nerve and the ganglionar cells. Comparisons were made between baseline and the 1st week, 1st and 6th month and 1st year. (STATISTICA, StatSoft Inc. Tulsa, Oklahoma, USA).

Results: We studied 12 patients (19 affected eyes) (5 men/7 women); mean age of 29.8 ± 12.9 years. The underlying diseases were systemic lupus erythematosus (n=1), neuromyelitis optica (n=1), neuroretinitis (n=1), relapsing polychondritis (n=1), pars planitis (n=1), Behçet's disease (n=2) and idiopathic (n=5). Before biological treatment and besides oral corticosteroids, patients had received intravenous (IV) methylprednisolone boluses (n=9), cyclosporine A (n=1), cyclophosphamide (n=2), mycophenolate (n=2), hydroxychloroquine (n=1), methotrexate (n=8) and azathioprine (n=5). Biological treatment was based on rituximab (n=2) (2 IV, doses of 1 g/very 2 weeks and every 6 months), adalimumab (n=5) (40 mg/1-2 week), tocilizumab (n=4) (8 mg/kg/2-4 weeks) and infliximab (n=3) (5 mg/kg at 0, 2 and 6 week and then every 8 weeks). The characteristics of the 12 patients are shown in the TABLE.

After biological treatment we observed an improvement in the ocular parameters: VA [0.66±0.32 to 0.84±0.29; p= 0.03], OCT of the optic nerve [123.20±58.28 to 190.54±175.38; p= 0.11], and OCT of the ganglionar cells [369.55±137.37 to 270.67±23.21; p= 0.03] at one year. After a mean follow-up of 29.09 ± 19.23 months, there were no severe adverse effects.

Conclusion: Biologic therapy in NION idiopathic or associated to IMIDs, refractory to conventional treatment, seems to be effective.

Case	Sex/Age (years)	Underlying disease	Laterality	Immunosuppressive drugs before biological therapy	Biological therapy
1	Man/29	Idiopathic	Right	AZA	TCZ
2	Man/26	Idiopathic	Bilateral	AZA	TCZ
3	Man/21	Idiopathic	Bilateral	MTX, AZA	ADA
4	Woman/25	Behçet's disease	Right	MTX, CyA	ADA
5	Woman/39	Behçet's disease	Right	MTX, MMF	IFX
6	Woman/14	Neuroretinitis	Bilateral	MTX	ADA
7	Man/56	SLE	-	Hydroxychloroquine, MMF, CFM	RTX
8	Woman/43	Neuromyelitis optica	Bilateral	AZA	RTX
9	Man/43	Relapsing polychondritis	Bilateral	MTX, CyA	IFX, TCZ
10	Woman/24	Pars planitis	Bilateral	MTX, AZA	ADA
11	Woman/13	Idiopathic	Bilateral	MTX	ADA
12	Woman/25	Idiopathic	Bilateral	MTX	IFX, TCZ

ADA: adalimumab, AZA: azathioprine, CFM: cyclophosphamide, CyA: cyclosporine A, HCO: hydroxychloroquine, IFX: infliximab, MMF: mycophenolate, MTX: methotrexate, RTX: rituximab, SLE: systemic lupus erythematosus, TCZ: tocilizumab

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