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INCREASED FREQUENCY OF ANTI-MA2 ENCEPHALITIS ASSOCIATED WITH IMMUNE CHECKPOINT INHIBITORS

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Abstract:

Introduction: *Therapy with monoclonal antibodies (Abs) targeting immune checkpoints, including cytotoxic T lymphocyte–associated antigen 4 (CTLA-4), the programmed death-1 receptor (PD-1), and its ligand PD-L1, has led to a paradigm shift in the treatment of numerous types of cancer.* ***Aims and objective:*** *The basic aim of the study is to analyse the increased frequency of anti-Ma2 encephalitis associated with immune checkpoint inhibitors.* ***Material and methods:*** *This descriptive study was conducted in Baqai Medical University, Karachi During March 2019 till November 2019. Data was collected from those patients who observed with anti-Ma2-PNS after treatment with ICIs. All patients underwent a comprehensive laboratory examination for suspected PNS. Demographic and clinical features of patients with Ma2-PNS triggered by ICIs were compared with those of the overall cohort of patients with Ma2-PNS unrelated to ICI treatment diagnosed in hospital.* ***Results:*** *Most of the patients were male (83%), with a median age of 63 years (range: 47–79 years). All were Caucasians. Four of them had an associated non–small-cell lung cancer, 1 a pleural mesothelioma, and the last one a renal clear cell carcinoma. At the time of ICI introduction, a median of 6.5 months (range: 0.5–25) after cancer diagnosis, all the patients except 1 (patient 2) had a metastatic disease, which included brain involvement in 2 cases.* ***Conclusion:*** *It is concluded that motor neuron involvement could complicate Ma2-Ab-associated PNS in almost 10% of patients and must be carefully studied to adapt treatment.*

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INTRODUCTION

Therapy with monoclonal antibodies (Abs) targeting immune checkpoints, including cytotoxic T lymphocyte–associated antigen 4 (CTLA-4), the programmed death-1 receptor (PD-1), and its ligand PD-L1, has led to a paradigm shift in the treatment of numerous types of cancer. Their unprecedented results in controlling tumors at a metastatic stage have come at the expense of an increased risk of developing immune-related adverse events (irAEs), including severe neurologic complications [1].

Given their mechanism of action, a possible association with the development of paraneoplastic neurologic syndromes (PNSs) has been predicted. Recently, the emergence of individual cases and small series of patients developing encephalitis and other neurologic manifestations has caused growing concern [2]. Because an increasing number of patients will be exposed to immune checkpoint inhibitors (ICIs) in the forthcoming future, it is crucial to identify the main features of neurologic irAEs [3].

PNS with Abs targeting the intracellular Ma2 antigen characterizes a peculiar form of encephalitis with prominent involvement of limbic, brainstem, and diencephalic structures, usually in association with testicular or lung cancer[4]. Atypical manifestations including narcolepsy-cataplexy, weight gain, sexual dysfunction, and motor neuron syndrome were described and account for the difficulty in diagnosing anti–Ma2 antibody–associated PNS (Ma2-PNS) [5].

Immune-checkpoint inhibitors (ICIs) constitute a novel class of agents recently approved to treat a number of human malignancies. Due to their immunomodulatory mechanism of action, ICIs can generate a wide range of immune-related adverse events (irAEs) of which neurological toxicities are of special interest because of their potential severity. Patients with advanced malignancies treated with immune checkpoint inhibitors are at increased risk for developing immune-related neurological complications [6].

It is a phenomenon of immunological twist when immunotherapy against co-stimulatory molecules activates previously normal T cells to kill tumor cells but, in so doing, the T cells become unrestrained, triggering other autoimmune diseases for which conventional immunotherapy is needed. The most common autoimmune neurological diseases, usually occurring within 2-12 weeks after immune checkpoint inhibitor initiation, include: inflammatory myopathies, myasthenia gravis, acute and chronic demyelinating polyradiculoneuropathies, vasculitic neuropathies, isolated cranial neuropathies, aseptic meningitis, autoimmune encephalitis, multiple sclerosis and hypophysitis. The neurological events can evolve rapidly, necessitating the need for vigilance at all stages of treatment, even after completion, because early immunotherapeutic interventions are effective [7].

Aims and objective

The basic aim of the study is to analyse the increased frequency of anti-Ma2 encephalitis associated with immune checkpoint inhibitors.

MATERIAL AND METHODS:

This descriptive study was conducted in Baqai Medical University, Karachi During March 2019 till November 2019. Data was collected from those patients who observed with anti-Ma2-PNS after treatment with ICIs. All patients underwent a comprehensive laboratory examination for suspected PNS. Demographic and clinical features of patients with Ma2-PNS triggered by ICIs were compared with those of the overall cohort of patients with Ma2-PNS unrelated to ICI treatment diagnosed in hospital.

Statistical analysis

Categorical data were analysed with the Fisher exact test (2 tailed) and numerical data with the Mann-Whitney *U* test. Statistical analyses were performed using IBM SPSS Statistics Software. P-Values <0.05 were considered significant.

RESULTS:

Most of the patients were male (83%), with a median age of 63 years (range: 47–79 years). All were Caucasians. Four of them had an associated non–small-cell lung cancer, 1 a pleural mesothelioma, and the last one a renal clear cell carcinoma. At the time of ICI introduction, a median of 6.5 months (range: 0.5–25) after cancer diagnosis, all the patients except 1 (patient 2) had a metastatic disease, which included brain involvement in 2 cases.

All the patients in the present study were investigated using brain MRI, which showed bilateral fluid-attenuated inversion recovery hyperintensity involving the mesial temporal lobes in 4 cases, including 1 with coexisting hyperintensity of the periventricular regions of the third ventricle and hypothalamus.

Table 01: Characteristics of patients with ICI-induced Ma2 antibody paraneoplastic syndrome

Table Characteristics of patients with ICI-induced Ma2 antibody paraneoplastic syndrome

Patient no.	Sex, age (y)	Cancer (interval from diagnosis to ICI initiation)	ICI treatment (interval from ICI initiation to neurologic syndrome onset)	Neurologic symptoms/signs	Brain MRI, inflammatory alterations/type	CSF (white cells per mm^3)/ protein [g/L]/ OCB)	Ma2 Ab CSF (titer)/ serum (titer)	PNS treatment	mRS score before and after PNS treatment (length of follow-up)
1	M, 79	Stage IV lung cancer (9 mo)	Pembrolizumab (2 mo)	Onset: altered behavior with impulsivity and disinhibition, hyperphagia Plateau: confusion and decreased consciousness (GCS 11)	Absent	n (0)/↑/NA	+(1: 1,280)/+(1: 64,000)	Corticosteroids	5 → 3 (6 mo)
2	M, 71	Pleural mesothelioma (0.5 mo)	Nivolumab + ipilimumab (5 mo)	Narcolepsy-cataplexy, hyperphagia and weight gain (+12 kg over 6 mo), psychiatric symptoms	FLAIR hypersignal involving the uncus bilaterally, periventricular regions of the third ventricle and hypothalamus	↑/↑ (0.74)/-	+(1: 1,280)/+(1: 1,024,000)	Corticosteroids Rituximab	3 → 6 (6 mo)
3	F, 57	Stage IV lung cancer (8 mo)	Nivolumab (8 mo)	Memory deficits, new-onset epilepsy, and psychomotor retardation	FLAIR bilateral MTL hypersignal	↑ (10)/↑ (0.79)/-	+(1: 40,960)/+(1: 2,048,000)	Corticosteroids IVIG	3 → 6 (4 mo)
4	M, 47	Stage IV lung cancer (1 mo)	Pembrolizumab (8 mo)	Abrupt onset of diplopia Plateau: ophthalmoplegia + head drop	FLAIR bilateral MTL hypersignal	n (2)/n (0.38)/+	+(NA)/+(NA)	Corticosteroids	4 → 6 (4 mo)
5	M, 55	Stage IV kidney cancer (25 mo)	Nivolumab (3 mo)	Abrupt onset of right ear hearing loss, followed by ataxia, vertigo, and memory deficits Plateau: hyperphagia, weight gain (+18 kg in 3 mo) excessive daytime sleepiness	FLAIR bilateral MTL hypersignal	n/↑ (0.92)/NA	+(NA)/+(NA)	Corticosteroids PLEX	4 → 4 (3 mo)
6	M, 69	Stage IV lung cancer (5 mo)	Nivolumab (3 mo)	Confusion and focal seizures Plateau: confusion and decreased consciousness (GCS 13)	Absent	n (5)/↑ (0.60)/ NA	+(1: 40,960)/ NA	Corticosteroids	4 → 6 (1 mo)

Abbreviations: FLAIR = fluid-attenuated inversion recovery; ICH = immune checkpoint inhibitor; IVIG = IV immunoglobulin; mRS = modified Rankin Scale; MTL = mesial temporal lobe; n = normal; NA = not available/not performed; OCB = oligoclonal band; PLEX = plasmapheresis.

Reference by: Alberto et al., 2019

DISCUSSION:

Despite these differences, the inflammatory alterations detected by CSF analysis, the presence of well-characterized Abs, and the selective brain MRI involvement of the mesial temporal lobe and diencephalon structures strongly suggest an immune-mediated pathogenesis. We therefore consider that the ICI treatment elicited the autoimmune encephalitis in our patients [8].

Because the anti–Ma2-associated syndrome is characterized by atypical manifestations such as increased daytime sleepiness, hyperphagia, and weight gain, it is important for the clinician to recognize the prominent features of this disease to avoid diagnostic pitfalls. These symptoms are related to the diencephalic involvement and need to be promptly differentiated from the clinical correlate of primary hypothyroidism, which is a much more common irAE that shares a similar presentation [9].

The latter misdiagnosis occurred in 1 patient that we present (patient 2). Clinical worsening despite thyroid hormone therapy prompted further investigations until a final diagnosis of polysomnography-proven narcolepsy-cataplexy was finally made, together with the discovery of low hypocretin levels in the CSF. Patients treated with cancer immunotherapy are also at an increased risk of developing hypophysitis, which is less frequent than primary hypothyroidism and more difficult to diagnose, presenting mainly with fatigue, hormonal disturbances, and headache [10].

Diagnostic delay could result in inappropriate continuation of ICI therapy and late introduction of immunosuppressants, with obvious repercussions on patients' status. Indeed, the clinical outcome of patients with Ma2 Ab was poor, with most of the patients dying due to the neurologic involvement, and the remainder being left severely disabled [1]. To this matter, we would like to underline that (1) contrary to previous reports, we demonstrate that ICI-related encephalitis can develop beyond the first 4–8 weeks of treatment and (2) ICI withdrawal and administration of corticosteroids, which is the recommended course of treatment in this situation,[19] is not sufficient for all patients; (3) the adoption of second-line immunosuppressants is probably warranted for refractory cases [11].

CONCLUSION:

It is concluded that motor neuron involvement could complicate Ma2-Ab-associated PNS in almost 10% of patients and must be carefully studied to adapt treatment. Patients with preexisting Abs are probably at an increased risk of developing

irAEs, as demonstrated for anti-acetylcholine receptor autoantibodies and subsequent myositis in patients treated with avelumab.

REFERENCES:

1. Touat M, Talmasov D, Ricard D, Psimaras D. Neurological toxicities associated with immune-checkpoint inhibitors. Curr Opin Neurol 2017;30:659–668.
2. Graus F, Dalmau J. Paraneoplastic neurological syndromes in the era of immune-checkpoint inhibitors. Nat Rev Clin Oncol Epub 2019 Mar 12.
3. Williams TJ, Benavides DR, Patrice KA, et al. Association of autoimmune encephalitis with combined immune checkpoint inhibitor treatment for metastatic cancer. JAMA Neurol 2016;73:928.
4. Dalmau J. Clinical analysis of anti-Ma2-associated encephalitis. Brain 2004;127:1831–1844.
5. Vogrig A, Joubert B, Maureille A, et al. Motor neuron involvement in anti-Ma2-associated paraneoplastic neurological syndrome. J Neurol 2019;266:398–410.
6. Dauvilliers Y, Bauer J, Rigau V, et al. Hypothalamic immunopathology in anti-Ma-associated diencephalitis with narcolepsy-cataplexy. JAMA Neurol 2013;70:1305–1310.
7. Adams C, McKeon A, Silber MH, Kumar R. Narcolepsy, REM sleep behavior disorder, and supranuclear gaze palsy associated with Ma1 and Ma2 antibodies and tonsillar carcinoma. Arch Neurol 2011;68:521–524.
8. Waters P, Pettingill P, Lang B. Detection methods for neural autoantibodies. Handb Clin Neurol 2016;133:147–163.
9. Rosenfeld MR, Eichen JG, Wade DF, Posner JB, Dalmau J. Molecular and clinical diversity in paraneoplastic immunity to Ma proteins. Ann Neurol 2001;50:339–348.
10. Graus F, Delattre JY, Antoine JC, et al. Recommended diagnostic criteria for paraneoplastic neurological syndromes. J Neurol Neurosurg Psychiatry 2004;75:1135–1140.
11. Voltz R, Gultekin SH, Rosenfeld MR, et al. A serologic marker of paraneoplastic limbic and brain-stem encephalitis in patients with testicular cancer. N Engl J Med 1999;340:1788–1795.