

Case Report

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Pembrolizumab and Campylobacter Jejuni Induced Guillain-Barré Syndrome in a Patient with Advanced Duodenal Adenocarcinoma: A Case Report and Literature Review

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ABSTRACT

Neurological Immune Related Adverse Events (irAEs) secondary to Immune Checkpoint Inhibitors (ICI) are uncommon with an incidence of 1% to 5%. Among them, the Guillain Barré syndrome may be life-threatening and must be diagnosed early. We describe a clinical case of Guillain Barré Syndrome with a concomitant Campylobacter Jejuni colitis occurring after the first intravenous injection of pembrolizumab. A review of literature regarding the Guillain Barré syndrome after ICI use is added as a complementary source.

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Introduction

Pembrolizumab, a humanized immunoglobulin G4 monoclonal antibody belongs to the Immune Checkpoint Inhibitors (ICI) family. Pembrolizumab interacts with the receptor PD-1 expressed on lymphocytes, blocking the link with its ligand PD-L1, then releasing the reactivation of cytotoxic T-cells [1, 2].

ICI are well tolerated with few grade 3-4 Immune Related Adverse Events (IR AEs). According to the ESMO guidelines 2022, the most frequent toxicities are Immune Related Cutaneous AEs (IRCAEs), 50% all grades, but rarely severe, followed by IR-endocrinopathies, i.e hypothyroidism (6-9%), hypophysitis (1 %), and adrenal insufficiency (1-2 %). Other toxicities are observed, such as diabetes mellitus with insulin dependence (1-2%), and hepatitis (grade 3 1%-2%) [3]. Overall, the toxicity rates increase when anti-PD-1/PD-L1 antibodies are delivered in combination with anti-CTLA-4 antibodies, such as ipilimumab.

The incidence of neurological Immune Related Adverse Events (irAEs) is low with a range of 1%-5%. A large variety of neurological irAEs have been described, including encephalitis, aseptic meningitis for the central nervous system but also acute or chronic demyelinating polyneuropathy, cranial nerve neuropathy, myasthenic syndrome and myositis for the peripheral nervous system [3, 4].

ESMO's guidelines 2022 mention that neuromuscular disorders account for approximatively 50% of neurological irAEs, which primarily pool myositis, myasthenia gravis, demyelinating polyradiculoneuropathy and overlapping syndromes [3]. Immune

related neuropathies are mostly demyelinating and may present as an acute polyradiculoneuritis (Guillain Barré Syndrome) with an incidence of 0.2%-0.4%. Anti- ganglioside antibodies are usually described as negative [3]. According to ESMO's guidelines, CSs (corticosteroids) are initially recommended and associated with a favorable outcome. If corticosteroids are unsuccessful, Intravenous Immunoglobulin (IVIG) is an additional or alternative treatment. A permanent discontinuation of ICI is highly recommended in case of grade 3-4 IR neurotoxicity [3].

In this report, we present the clinical case of a patient with Guillain-Barré syndrome after treatment with one dose of pembrolizumab for a microsatellite instability-high (MSI-H) locally advanced duodenal adenocarcinoma.

Case Report

A 69-year-old man was hospitalized for anemia caused by a digestive bleeding. A gastro esophageal endoscopy showed a hemi-circumferential ulcerated lesion with budding edges localized in the duodenal bulb. Biopsies were in favor of a moderately differentiated adenocarcinoma with a concurrent loss of MLH1 and PMS2 immunoeexpression.

A CT-scan evaluation confirmed the locally advanced disease without metastatic dissemination. Surgery was contraindicated due to unstable angina and moderate to severe calcific aortic stenosis. According to MSI status, a first intra-veinous infusion of pembrolizumab 200 mg was performed at day 1. At day 18, the patient suffered from grade 3 diarrhea with more than ten stools per day, a weight loss of 8 kg in three weeks and grade 3 asthenia according to Common Terminology Criteria for Adverse Events (CTCAE). There was no fever. An abdominal CT-scan showed colitis with symmetric, diffuse thickening of the rectum, sigmoid,

and ascending colon. Recto-sigmoidoscopy was not done. No stool culture was done. However, a Campylobacter Jejuni serology was in favor of a recent infection, as confirmed by the presence of IgG (37,15U/ml) and IgM (70U/ml).

Diarrhea was treated with intravenous (IV) methylprednisolone 2mg/kg per day, loperamide and IV hydration. At day 28, the patient exhibited progressive proximal tetraparesis and distal paresthesia leading to the diagnosis of severe Guillain-Barré syndrome as the patient had lost the ability to walk. The ONLS (Overall Neuropathy Limitations Scale) score was at 11/12. There was no respiratory impairment. An electroneuromyography showed a large decrease of motor nerve amplitudes with discrete demyelinating abnormalities contrasting with sensitive nerve amplitudes conservation raising an acute motor axonal neuropathy (AMAN).

Serum antibodies against gangliosides, AntiGM1 (IgG), antiGD1a (IgG and IgM) and antiGT1b (IgG) were positive.

Intravenous immunoglobulin, 2mg/kg for 3 days and intravenous corticosteroids (IV methyprednisolone 240mg for 5 days) were administrered, followed by oral prednisolone 80mg per day. Pembrolizumab was definitively interrupted.

An electroneuromyography was done three weeks later and concluded to a worsening of the sensitive and motor amplitude especially for the lower members and stability for the upper members. The CT-scan made three months later, knowing that pembzolzizumab was definitively interrupted, unfortunately showed an increase of the duodenal lesion and a dissociated response on the lymph nodes. There was no new metastatic lesion observed.

At 4.5 months, the neurologic evaluation concluded to an asymmetric improvement of the motor symptoms in favor of the right side. A 2/5 motor deficit on the left levator muscles of the leg and 4/5 on the flexor muscles. Hip flexion was impossible on both sides. On the upper limbs, a 4/5 motor deficit persisted on the

left arm. An electroneuromyography was made and concluded to a moderate improvement of the sensitive and motor amplitude on the four limbs and a weak detection on multiple muscles including the proximal muscles.

Discussion

Guillain-Barré syndrome (GBS), an acute peripheral neuropathy, may be associated with permanent or long-term sequelae and occasional fatality. Acute infectious illnesses precede 50%-75% of the GBS cases. Although many infectious agents have been associated with GBS, the strongest documented association is with Campylobacter infection. The association was first reported by Rhodes and Tattersfield in 1982. In a systematic review of published studies, approximately 30% of cases of GBS had evidence for preceding infection with Campylobacter jejuni. In terms of pathogenesis, activated macrophages and T cells and serum antibodies against gangliosides are observed but their significance is unclear [3-8].

In our knowledge, few cases were published reporting Guillain-Barré syndrome or Guillain-Barré like-syndrome induced by pembrolizumab Table 1. One case was associated with Stevens-Johnson Syndrome leading to death after respiratory complications [9]. All cases occurred at the beginning of the treatment: from the first to the fifth injections. Guillain-Barré syndrome was also described with others ICI such as nivolumab Table 2.

Most of the time, the ICI was used as monotherapy Table 1. All patients were treated with corticosteroids and intravenous immunoglobulins except for one patient who received immunoglobulins and plasma exchange. Acyclovir was prescribed in one case because of a concomitant Ramsay Hunt syndrome. Neurologic recovery was variable and uncertain. Tumoral response to ICI, when described, was observed and prolonged, emphasizing the concept of high efficacy of ICI after grade 3-4 related toxicities. One case described by Aoki et al., showed a complete response of a stage IV urothelial carcinoma 6 months after the last dose of pembrolizumab [10].

Table 1: Review of literature regarding the Guillain Barré syndrome after pembrolizumab

	Brzezinska BN et al. [11]	Hashimoto Ret al. [12]	Aoki S et al. [10]	Oguri Tet al. [13]	Vikram Sangani et al. [14]	Han C et al. [15]	Ong S et al. [16]	de Maleissye MF et al. [17]	de Maleissye MF et al. [17]
Age (years)	72	74	85	76	80	55	66	45	85
Associated diarrhea	No	No	No	No	No	No	No	No	No
Associated treatment	Lenvatinib	None	None	None	None	Sunitinib	None	None	Preceded by ipilimumab and binimetinib
Cancer localisation	Endometrial adenocarcinoma	Non small cell lung cancer	Urothelial carcinoma	Lung carcinoma	Bladder cancer	Renal clear cell carcinoma with sarcomatoid differentiation	Lung adenocarcinoma	Nasal cavity melanoma	Metastatic melanoma
Date of publication	2021	2020	2020	2021	2021	2020	2018	2016	2016
Man (M) / Woman (W)	W	M	W	W	M	M	M	W	W
Neurologic recovery	Favorable	Undescribed	Favorable	Death from respiratory failure at day 53	Favorable	Favorable	Favorable	Favorable	Favorable
Number of cycles before toxicity	2	1	5	1	1	5	2	2	6
Other toxicities	None	None	None	Stevens-Johnson Syndrome/Toxic Epidermal Necrosis	None	None	None	None	None
Respiratory complication	No	No	No	Yes	No	No	No	No	No

Tumor response	Undescribed	Undescribed	Complete response at 6 months	Undescribed	Undescribed	Partial response	Undescribed	Undescribed	Complete response at 6 months
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Table 2: Review of literature regarding the Guillain Barré syndrome after nivolumab.

	McNeill CJ et al. [18]	Jacob A et al. [19]	Sakoh T et al. [20]	Schneiderbauer R et al. [21]	Pierrard J et al. [22]	Fukumoto Y et al. [23]	Kyriazoglou A et al. [24]	Mazzaschi G et al. [25]	Tanaka R et al. [26]	Nukui T et al. [27]
Date of publication	2019	2016	2019	2017	2019	2018	2019	2018	2016	2018
Man (M) / Woman (W)	M	W	M	M	M	M	M	W	W	M
Age (years)	68	68	72	51	70	66	74	80	85	45
Cancer localisation	Colorectal	Lung squamous cell carcinoma	Lung carcinoma	Melanoma	Urothelial carcinoma	Lung carcinoma	Urothelial carcinoma	Lung adenocarcinoma	Melanoma	Nasal cancer
Number of cures before toxicity	4	3 months of treatment	13	5 months of treatment	29	2	3	3	2	Not available
Associated treatment	None	None	None	None	None	None	None	None	None	None
Associated diarrhea	No	No	No	No	No	No	No	No	No	No
Respiratory complication	Yes	Yes with oral intubation	No	No	No	No	No	No	No	No
Neurologic recovery	Partial recovery	Undescribed	Undescribed	Partial recovery	Complete recovery	Undescribed	Partial recovery	Complete recovery	Partial recovery with steroid dependance	Undescribed
Other toxicities	None	Death within 11 days	Ramsay Hunt syndrome	None	Adrenocorticotrophic hormone deficiency after C11	None	None	None	None	None
Tumor response	Undescribed	Undescribed	Partial response	Undescribed	Undescribed	Undescribed	Undescribed	Remarkable disease response after 6 months	Stability	Undescribed

The originality of this present case is the clinical sequence of pembrolizumab administration followed by Campylobacter Jejuni colitis and Guillain-Barré syndrome. Campylobacter is otherwise known to cause acute motor axonal neuropathy which is an axonal classification of Guillain-Barré syndrome. Diarrhea with colitis is one of the major adverse events observed with ICI, anti-PD-1 or PD-L1 and anti-CTLA4. According to the ESMO grade 3-4 colitis should be explored by stool testing for enteropathogenesis, Clostridium Difficile toxins, faecal calprotectin or lactoferrin, whole blood PCR for cytomegalovirus, complete blood count, serum C-reactive protein and electrolytes, interferon-gamma release assay, hepatitis A, B, C and E end human immunodeficiency virus tests and endoscopic evaluation. ICI therapy is recommended associated with IV methylprednisolone 1mg/kg/day switched to prednisolone 1mg/kg/day after 3 to 5 days.

Because of its scarcity, no data was available regarding re-introduction of ICI after immunotherapy-induced Guillain-Barré syndrome.

In 2019, Gravbrot et al [28]. reported a case of a 71-year-old gentleman who developed a Guillain-Barré after three cycles of ipililumab (cytotoxic T lymphocyte antigen-4 inhibitor) in adjuvant therapy for stage IIIB melanoma. Ipilimumab was discontinued and few months later, he was treated with pembrolizumab for a recurrent disease. A complete response was observed with pembrolizumab, and no toxicity was reported [29, 30].

Conclusion

Immune-related adverse events (irAEs) involving the nervous system must be known by medical oncologists because of growing use of immunotherapy in solid tumors. In this case, a Guillain-Barré

syndrome was observed after Campylobacter Jejuni colitis occurring after one cycle of pembrolizumab. It underlines the absolute necessity to early manage gastro-intestinal immune toxicities in order to avoid rare life-threatening neurological toxicities.

Conflict of Interest and Consent

The authors have no conflict of interest to declare. Written informed consent was obtained from the patient to publish this report in accordance with the journal’s patient consent policy.

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