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Case Report

Outcome of patient with myasthenia gravis with the use of immunotherapy in metastatic Merkel cell carcinoma

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Abstract

We report on a 79-year-old man diagnosed with localized Merkel cell carcinoma (MCC) who also had acetylcholine receptor antibody (Ach-R-Ab)-positive myasthenia gravis (MG) controlled on prednisolone, mycophenolate and intravenous immunoglobulin (IVIG). His MCC was initially treated with radiation, followed by chemotherapy on metastatic recurrence. Chemotherapy initially stabilized the disease, but he experienced significant fatigue and his disease progressed within 3 months. After careful consideration of the risk of a myasthenic crisis, he was commenced on avelumab. He had initial partial response, though he ultimately developed progressive disease which led to a decision for best supportive care at 10 months post starting immunotherapy. Importantly, as per spirometry, his MG remained stable throughout immunotherapy. We present the current case to demonstrate that MG should not be viewed as an absolute contraindication to immunotherapy in scenarios where there are limited alternate therapeutic options.

Keywords: oncology, neurology

INTRODUCTION

Merkel cell carcinoma (MCC) is a rare and aggressive neuroendocrine skin cancer with a 5-year-survival rate <20%. Although exquisitely radiosensitive, it is only relatively chemosensitive with a 55% response rate in the first-line setting with median duration of response of 2–8 months [1]. Peptide receptor radionuclide therapy (PRRT) has increasing evidence, though this is limited to MCCs with high somatostatin receptor expression. In the second-line setting, the JAVELIN trial demonstrated that avelumab (anti-PD-L1) had objective response rates of 33%, with 74% of responses lasting more than 1 year [2], leading to immunotherapy becoming a mainstay of treatment. In patients with a pre-existing autoimmune condition, the risks of a flare in the autoimmune condition need to be carefully weighed against potential cancer control. There is scant evidence regarding the use of immunotherapy in patients with pre-existing myasthenia gravis (MG).

CASE REPORT

A 79-year-old gentleman presented in December 2018 with a rapidly growing right parotid mass that was ^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography (PET) avid. Core biopsy demonstrated a high-grade tumour with neuroendocrine differentiation favouring metastatic MCC of unknown primary. He completed definitive intent radiotherapy (63 Gray in 30 fractions) in April 2019. Repeat FDG-PET in July 2019 demonstrated marked decrease in size and avidity of the parotid lesion, though a new hypermetabolic liver lesion was detected. Liver biopsy demonstrated metastatic MCC similar to the original core biopsy specimen. He underwent stereotactic body radiation therapy (30 Gray in 3 fractions) to the liver lesion and subsequent FDG-PET demonstrated decreased avidity in the liver and new sites of disease (Fig. 1).

Our patient had MG diagnosed in June 2018 after developing progressive weakness with normal creatinine kinase, positive ACh-R-Ab and confirmatory single-fibre electromyography. This was managed by his neurologist with prednisolone, intravenous immunoglobulin (IVIG) and mycophenolate (Fig. 2). He was diagnosed with prostate cancer in 2002, which was treated with definitive radiotherapy, and he remained in remission as confirmed with persistently negative prostate-specific antigen making a paraneoplastic MG highly unlikely. He mobilized with a walking stick, required some assistance with personal care, but had greater subjective sense of fatigue than clinical fatigable weakness from MG.

His ^{68}Ga-DOTATATE PET scan revealed multiple sites of DOTATATE non-avid, FDG avid MCC and thus PRRT was not a therapeutic option. Due to concerns of giving immunotherapy with his underlying MG, he proceeded with single-agent carboplatin (rather than carboplatin/etoposide due to his functional status) in November 2019.

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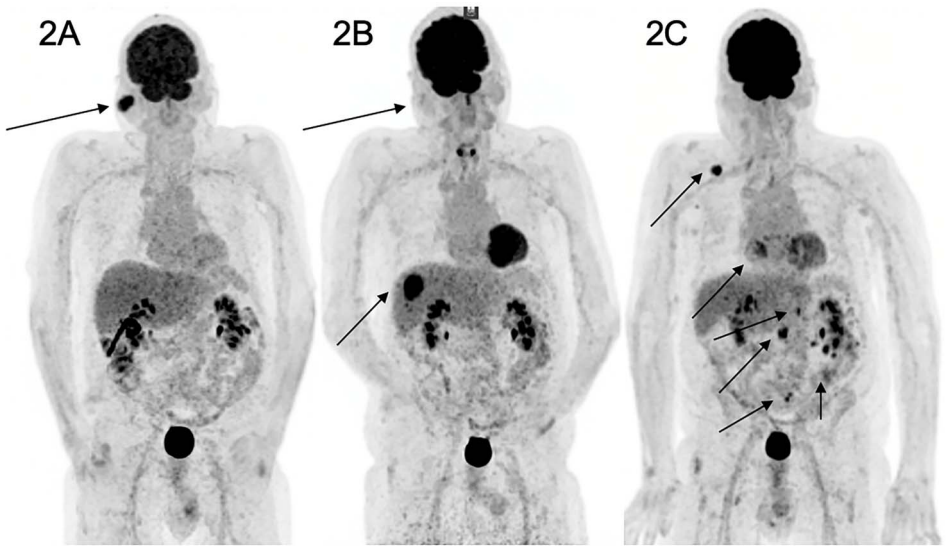

Figure 1. Serial FDG-PET imaging as presented with serial maximal intensity projections (MIPs). (**A**) (Jan 19): FDG avid lesion in the right parotid (arrow). (**B**) (Jul 19): Avidity in treated right parotid lesion is decreased, but there was interval development of a new hypermetabolic segment VII hepatic lesion. (**C**) (Oct 19): Avidity in the hepatic and parotid lesions is decreased, but there were multiple new sites of FDG avidity concerning for disease progression including a right superficial infrascapular mass, SUVmax 10.5 and a left para-aortic node level of T8, SUVmax 5.1 (and a smaller node posterior to this SUVmax 2.6). There are also multiple new abdominal masses, most prominently inferior to the duodenum, SUVmax 8.8, and several mesenteric and peritoneal (LHS > RHS) avid nodules with SUV max up to 9.5.

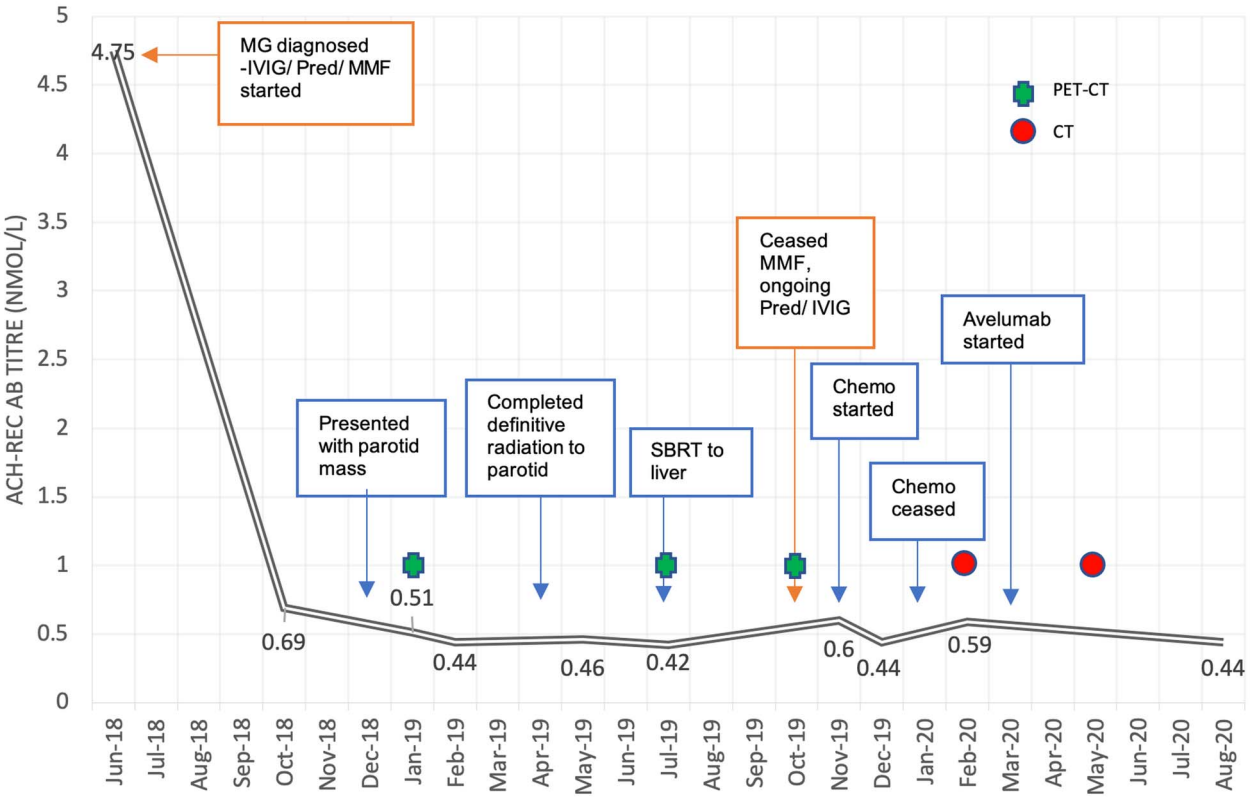

Figure 2. Timeline of the Ach-R-Ab titre alongside the main treatments of MCC, immunosuppressive agents used and timing of the radiographic restaging scans.

The chemotherapy was ceased in January 2020 due to thrombocytopenia and his Eastern Cooperative Oncology Group performance status dropping to 2. Repeat computed tomography (CT) in February 2020 demonstrated progressive intra-abdominal disease as well as a cerebellar lesion for which he received stereotactic radiosurgery. Discussion was conducted by both the oncologist and neurologist with the patient regarding the risk of avelumab exacerbating his MG event to the point of death weighed by the fact that there were no other remaining treatment options. There was also a precedent case report successfully maintaining IVIG to control

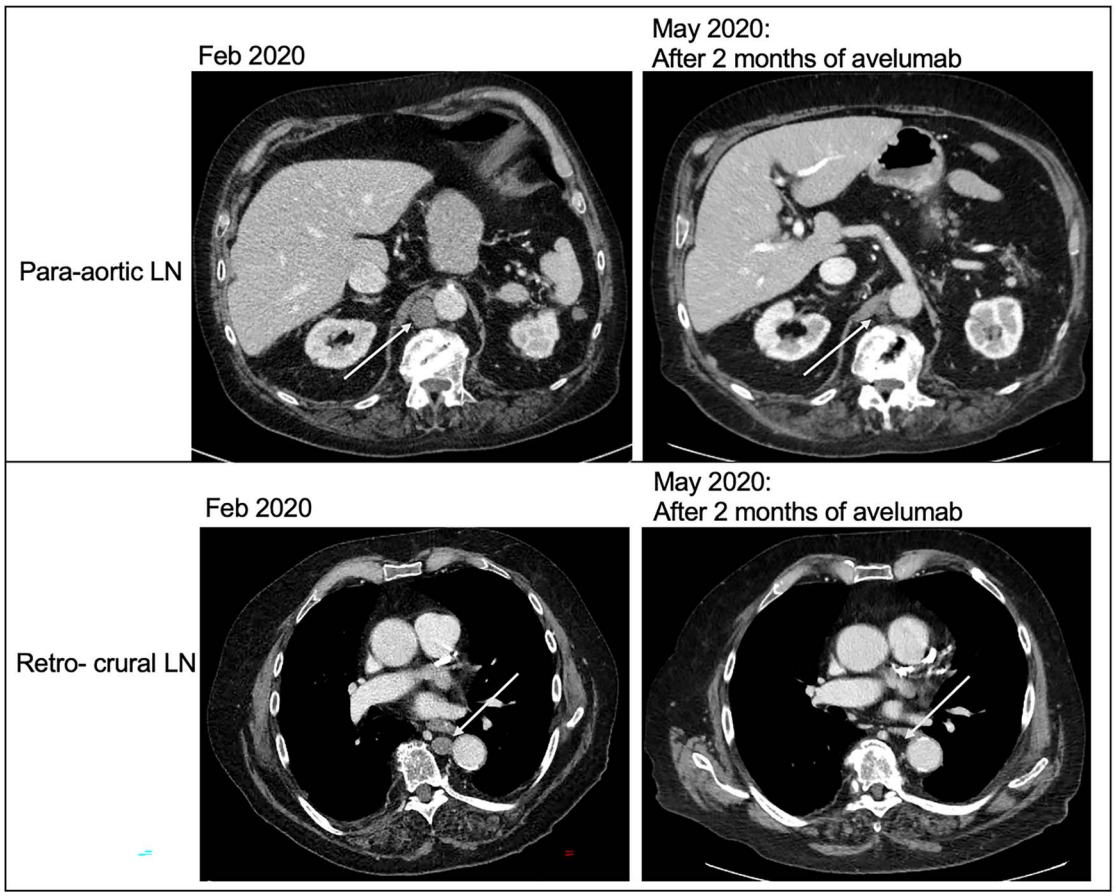

Figure 3. Serial CT imaging (Feb 20, May 20) demonstrating effect of immunotherapy on para-aortic and retrocrural lymph node.

	Pre Avelumab	2 months of treatment (May20)	4 months of treatment (Jul 20)	5 months of treatment (Aug 20)	8 months of treatment (Nov 20)	10 months of treatment (Jan 21)
T8 level LN	15	4 (-73%)	0 (-100%)	0 (0%)	0 (0%)	0 (0%)
Retrocrural LN	19	11 (-42%)	<5 (->55%)	<5 (0%)	0 (<100%)	0 (0%)
Liver segment VII lesion	25	20 (-20%)	20 (0%)	26 (+30%)	18 (-31%) Post 5# EBRT	18 (0%)
L retroperitoneal fat			21	25 (+19%)	0 (-100%) Post 5# EBRT	0 (0%)
R prerenal soft tissue				32	23 (-28%)	0 (100%)
L peri renal soft tissue					12	41 (+341%)
Posterior pararenal						64 (new)
R posterior pararenal						74 (new)
Adjacent to R adrenal						30 (new)
	Baseline	Partial response	Partial response	Progressive disease	Partial response	Progressive disease

Figure 4. Areas of disease and their response to treatment (on CT). Value: Longest diameter in mm (% of change).

autoimmune disease concurrently with immunotherapy [3]. Given his desire to continue systemic treatment, he opted to proceed. After his first dose, he reported subjective fatiguability but was managing at home with no respiratory or swallowing issues. He had a progression-free survival (PFS) (from treatment initiation

to progression of MCC) of 4 months (Fig. 3). When CT in August 2020 showed progressive disease in two bilateral para-renal masses, he underwent five fractions of external beam radiotherapy to these lesions. They reduced in size initially, but CT in January 2021 demonstrated significant progressive disease, which led to cessation of avelumab (Fig. 4). He had no increase in dyspnoea and neurology review found no evidence of MG flare. He was treated with best supportive care and died in February 2021.

DISCUSSION

There is mounting evidence of the role of the Programmed cell death protein 1 (PD1)/Programmed death-ligand 1 pathway in the development of autoimmunity including in MG [4]. As the use of immunotherapy continues to rise, it safety and effect in patients with pre-existent autoimmune conditions are increasingly relevant.

The AIM-NIVO trial assessing the efficacy of nivolumab in patients with autoimmune disorders and advanced malignancies is due to be completed in 2022 which will increase our data in these patients, though we note MG is not included in this cohort. In a literature search, we found 27 cases of immunotherapy-related MG. A 2017 review reported 23 cases; 72.7% were *de novo* MG, 18.2% were exacerbations of pre-existent MG and 9.1% were exacerbations of subclinical MG [5]. There are four further published case reports, one with a partial response with no flare of MG and three cases who experienced a myasthenic crisis in the setting of immunotherapy treatment [6–8].

In a 2017 study of 52 patients on immunotherapy, 38% of patients with an underlying autoimmune disorder subsequently had a flare of their disorder. Of the patients who had a flare, 60% had active disease at time of treatment and 50% were on immunosuppression [9]. As titrated by his neurologist, while on immunotherapy, our patient was on a relatively low dose of prednisolone and while the cessation of mycophenolate was possible, escalation of IVIG was required. Retrospective studies have demonstrated that patients on immunosuppression at the start of anti-PD-1 treatment had lower response rate, PFS and overall survival compared to those not on immunosuppressants [10]. For our patient, the prednisolone and IVIG concurrent throughout the avelumab theoretically could have decreased the effect of the avelumab. However, there is a precedent case report whereby a patient with underlying Guillain–Barre syndrome was maintained on IVIG while achieving durable complete response of their metastatic colon cancer with pembrolizumab [3].

In the second-line setting, in line with the JAVELIN trial, our patient had 4 months of PFS on avelumab compared to median PFS of 61 days seen with second-line chemotherapy [1]. As such, rather than an autoimmune condition being a contraindication to immunotherapy, more data are needed to guide the immunosuppressant agents and doses, which can be used concurrently to enable therapeutic options for cancer, especially when all alternative options have been exhausted.

CONFLICT OF INTEREST STATEMENT

None declared.

FUNDING

None.

ETHICAL APPROVAL

Consent sought from patient.

CONSENT

Written consent has been received from patient.

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