Development of Ocular Predominant Myasthenia Gravis after Treatment with Pembrolizumab for Basal Cell Carcinoma: A Case Report and Literature Review

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Abstract

Programmed Death-1 (PD-1), expressed on T-cells binds to PD-L1 (Programmed Death Ligand-1) suppressing T-cell activity. The PD-1 inhibitors, nivolumab and pembrolizumab, are Food and Drug Administration approved for treatment of numerous cancer types. PD-1 inhibition is being investigated in patients with advanced Basal Cell Carcinoma (BCC). Anti-PD-1 treatment causes immune mediated Adverse Events (irAEs) with a 20% high grade toxicity rate. While neurologic irAEs are uncommon, Myasthenia Gravis (MG) is emerging as an important association with management not optimally defined. We present a case of pembrolizumab induced ocular predominant MG in a patient with BCC responsive to a prolonged course of steroids and Intravenous Immunoglobulins (IVIG). A literature review is performed.

Keywords: Myasthenia gravis; PD-1; Pembrolizumab; Immunotherapy

Introduction

Positive and negative checkpoints regulate immune activity [1]. PD-1 binds PD-L1 inhibiting T-cell activity. Disruption of PD-1 leads to T-cell activation and irAEs. Neurologic toxicities including the development of myasthenia gravis have been associated with the inhibition of PD-1 [2]. It is important to identify toxicities early and optimize treatment strategies. We present a patient with advanced BCC who developed pembrolizumab associated ocular predominant MG.

Case Presentation

A 65-year-old male presented in 2013 to his dermatologist with a skin colored nasal lesion slowly growing for three years. A biopsy demonstrated BCC. He refused resection and presented to medical oncology with a 3 cm ulcerative nasal lesion. Ulceration resolved following treatment with vismodegib, a hedgehog pathway inhibitor, but biopsy in 2015 showed residual nodular BCC. Refusing resection he was treated with 4995 centigray radiation therapy in 15 fractions. In 2016, biopsy of a new rough patch within the radiation area revealed infiltrative BCC. He restarted vismodegib stopping after six months because of renal insufficiency. Over the next ten-months, a 1-cm ulcerative area progressively increased to 2.8 cm × 2 cm.

Refusing surgery, he was treated with pembrolizumab (200 mg every 3 weeks) administered on July 18 and August 15, 2018. Three weeks later he developed generalized weakness, decreased oral intake and mild transaminitis. Pembrolizumab was held and intravenous hydration administered. A week later he presented with worsening fatigue, bilateral ptosis, difficulty focusing his vision, voice hoarseness (“like a cold”) and gait imbalance. Neurologic examination revealed moderate to severe ptosis, slightly worsened on prolonged up-gaze. Pupils were equal and reactive. Extraocular movements showed limitations in bilateral abduction (-2 in ophthalmology examination), bilateral adduction (-1), depression (-1) and elevation (-1). Neck flexion and bilateral deltoid strength were full and not fatigable. There was subtle hypophonia. Gait was slightly “waddling” and myopathic.

MRI of brain and orbits showed no intra-cranial lesions or leptomeningeal dissemination. Workup revealed elevated CPK 691 U/L (ULN 200 U/L), aldolase 21.2 U/L (ULN 10.3 U/L), creatinine 2.11 mg/dl (ULN 1.3 mg/dl), and mild elevation in titers of anti-striation antibodies (1:40 with normal <1:40) and GAD-65 antibody (5.6 U/ml with normal <5 U/ml). ACHR binding, ACHR blocking,
and ACHR modulating antibodies, Anti-MuSK, and an extensive paraneoplastic neuropathy panel was negative. Lyme antibody titer, TSH and Free T4 were normal RPR was reactive. Clinical impression was immune-mediated myositis with Ocular Myasthenia Gravis (OMG).

Treatment was initiated (day 1) with 1 mg/kg (100 mg) prednisone daily plus 2 g/kg Immunoglobulins (IVIG) over 3 days given concern that neuromuscular weakness may worsen transiently with steroids. After initial IVIG, he reported stronger voice, improved reading and walking with only residual subtle non-improved abduction (-1). IVIG was administered at week 8 to allow movements, with resolved up- and down-gaze limitations, and ophthalmologic examination showed improved extraocular motility.

Second IVIG course was administered. Prednisone taper continued at rate of 5 mg per week. He was hospitalized at week 7 for steroid myopathy. Repeat ophthalmologic examination showed improved extraocular movements, with resolved up- and down-gaze limitations, and improved abduction (-1). IVIG was administered at week 8 to allow for steroid taper at higher rate of 10 mg per week. At week 13, he described near normalized reading and walking with only residual subtle non-fatigable bilateral ptosis. Extraocular movements were full except for inability to fully bury his sclera bilaterally on abduction. Gait was narrow based, brisk, and steady. The prednisone taper continued until reaching 10 mg daily and then decreased to 5 mg daily for one month and was tapered to 10 mg daily and then decreased to 5 mg daily for one week and then every other night for 2 weeks. By week 16 he was at his neurologic baseline with steroids tapered off by week 18.

### Discussion

A PubMed search performed on May 10, 2019 with search terms “PD-1 myasthenia”, “PD-L1 myasthenia”, “nivolumab myasthenia” and “pembrolizumab myasthenia” yielded 37 case reports with one reporting four cases, two reporting two cases, and 15 review articles with three reporting a new case, 13 pre-clinical articles and three phase 1/2 clinical trials.

Review of the identified articles' reference found another case report and a series reporting two cases [3]. A Japanese database search documented 12 cases of nivolumab induced MG among 9869 treated patients, 3 of whom were previously reported in PubMed with two having myasthenia limited to ocular involvement [4]. Of the 48 individual cases reviewed, ocular predominant myasthenia was reported in 11 cases [5,6-8]. Others related to generalized MG with fatal outcomes in 16 patients (10 directly related to MG,
One report described a 65-year old male developing ocular myasthenia with diplopia and bilateral ptosis 10 days after the second nivolumab infusion [5]. He received pyridostigmine 45 mg every 6 hours with gradual complete resolution. Repetitive Nerve Stimulation (RNS) testing was normal and serum Anti-acetylcholine Receptor (AchR) and Muscle-Specific Tyrosine Kinase (MuSK) antibodies were undetected. Two cases involved elderly melanoma patients who developed ocular myasthenia 7 and 11 weeks after pembrolizumab initiation which resolved with steroids [6]. One case developed before the fourth pembrolizumab cycle and treated with prednisone 25 mg daily with mild improvement after 3 days. He received a fourth cycle of pembrolizumab while having ocular symptoms. Ptosis peaked by week 11 of treatment and completely resolved by fifth cycle. Steroids were tapered over 4 weeks. He completed 8 cycles of pembrolizumab with near complete oncologic response without new signs of myasthenia.

Case two presented with progressive bilateral ptosis following 2 cycles of pembrolizumab. RNS and Electromyography (EMG) were negative. She received intravenous methylprednisolone 500 mg daily for 5 days followed by a 4 week prednisone taper. Symptoms improved after 10 days. Pembrolizumab was discontinued given concern for bulbar dysfunction. The patient showed complete oncologic response 5 months later. Both cases were seronegative for AchR antibodies and lacked a pre-existing autoimmune disorder.

Another report described an 85-year old woman with melanoma who developed diplopia and bilateral ptosis following two pembrolizumab treatments [7]. She received IVIG 30 gram daily for 5 days, prednisone 100 mg daily for 7 days and pyridostigmine 90 mg daily with complete symptom resolution. Pembrolizumab was discontinued. She was maintained on monthly IVIG and daily prednisone but passed away from unrelated cardiac issues.

Two cases of MG were included within a nine case series of immunotherapy induced neurological complications including a 68 year old male with melanoma presenting with left sided ptosis and mild esophoria from ocular myasthenia 5 weeks after initiation of pembrolizumab (2 doses) [3]. Single fiber EMG showed pathological jitter and RNS showed abnormal decrement consistent with myasthenic syndrome. Serum AchR Ab was negative. Prednisone was started at 10 mg/day and he recovered neurologically. Prednisone was tapered over a month with pembrolizumab re-initiated after 6 weeks.

Another case of ocular predominant myasthenia involved an 83 year old male with lung cancer who presented with 10 days of narrowing visual field, easy fatigability of eyelid and eye movement, posterior neck myalgia and neck extensor weakness 4 weeks after starting pembrolizumab [8]. Exam findings were consistent with ocular predominant myasthenia, and, similar to our case, elevated CPK and aldolase, indicating myositis.

A case of ocular predominant MG has been described 4 weeks following initiation of nivolumab plus ipilimumab therapy in a 62 years old man with melanoma. Treatment with prednisone and pyridostigmine engendered complete neurological recovery in 6 weeks. Re-introduction of nivolumab caused no relapse on 2-month follow-up [9]. However, a case of fully recovered, pembrolizumab induced ocular and bulbar MG showed recurrence of myasthenic syndrome following PD-1 inhibitor rechallenge [10].

Onda et al. [11] reported the first case of pembrolizumab induced OMG associated with anti-titin antibodies, with muscle biopsies notable for necrotizing myopathy and tubular aggregates [11]. Acetylcholine receptor and MuSK antibodies, edrophonium test, and RNS were negative. The patient was treated with prednisolone with initial worsening followed by pulse steroid therapy resulting in complete recovery by 4 months.

Another case of pembrolizumab associated OMG with positive AchR antibodies exhibited rapidly worsening ocular defects. The patient was treated with IVIG and IV methylprednisolone given the rapid course and achieved partial recovery as early as the 4th day [12]. Another case involved a patient with pulmonary carcinoma developing multiple irAEs. The 82 year old male developed agranulocytosis and interstitial lung disease attributed to pembrolizumab, he subsequently developed ocular MG almost 6 weeks after the last pembrolizumab dose with elevated titers of ANA, anti-neutrophil antibodies as well as AchR Abs [13]. The first case of ocular predominant MG related to avelumab, an anti-PD-L1 monoclonal antibody, was reported in a 65 years old man with lung adenocarcinoma. Serologies were positive for Anti-AchR Abs. Symptoms responded to pyridostigmine and withdrawal of avelumab [14].

In the 12 cases of nivolumab-induced MG reported by Suzuki et al. [4,15] two had ocular myasthenia and were reported in separate case reports [4,15]. One case involved exacerbation of preexisting ocular MG [15]. The other involved the development of focal adjustment disorder, ptosis, and muscle weakness responsive to prednisone and pyridostigmine with complete remission in several weeks [4]. Nivolumab was restarted on day 179 without relapse of MG.

Ocular Myasthenia Gravis (OMG) is immune mediated and characterized by weakness and fatigability of the levator palpebrae superioris, orbicularis oculi, and oculomotor muscles. Ocular only involvement is seen in 15% of MG patients. Diagnostic and prognostic differences exist between OMG and generalized MG (GMG). AchR and MuSK antibodies are detected in 80% to 90% and 40% to 55% of GMG patients but only in 40% to 50% and <10% OMG patients. Only 4 of the 11 reported cases of immunotherapy induced OMG were seropositive for Anti-AchR antibodies as opposed to two-third of cases of immunotherapy induced generalized MG, with one case being associated with Anti-titin Abs [2]. RNS and single fiber EMG are less sensitive for diagnosing OMG compared to GMG being diagnostic only in 3 of the 11 cases mentioned in Table 1.

Idiopathic OMG is frequently managed symptomatically with acetylcholine esterase inhibitors and steroids. In immunotherapy induced OMG, complete resolution developed using oral steroids in five cases, with pyridostigmine alone being used in three cases, and IVIG plus high dose steroids in three cases (including our patient). Given the slow clinical response in our patient, the steroid taper was prolonged over 4 months. Concomitant myositis, myocarditis or serum CPK elevation is less frequently reported in predominant ocular myasthenia as compared to immunotherapy induced GMG [2]. Onset of symptoms developed 3 to 11 weeks after initiation of anti-PD-1 therapy. The patient presented here developed ocular predominant myasthenia early in the treatment course following 2 doses of pembrolizumab. Anti-PD1 therapy was safely re-instituted in about a third of ocular myasthenia cases without relapse.

Follicular helper T (Th) cells might be central to MG development. A population of circulating CD4(+)CXCR5(+)PD-1(+) Th cells present in OMG and GMG patients suggest an underlying role of...
PD-1 in myasthenia development [16]. Increased PD-1 expression on T-cells and PD-L1 on monocytes may reflect regulatory mechanisms modulating autoimmune MG [4,17].

We present a case and literature review of anti-PD-1 related ocular predominant myasthenia which carries a favorable prognosis compared to generalized myasthenia. These cases warrant close follow up with a low threshold to permanently discontinue therapy and start immunomodulation. Optimal steroid dosing and the role for IVIG and pyridostigmine in addition to the safety of immunotherapy rechallenge require elucidation.

References