CASE REPORT

A Case Report of Drug-Induced Myopathy Involving Extraocular Muscles after Combination Therapy with Tremelimumab and Durvalumab for Non-Small Cell Lung Cancer

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ABSTRACT

Recently developed anti-tumour therapies targeting immune checkpoints include tremelimumab and durvalumab. These agents have incompletely characterised side effect profiles. The authors report a 68-year-old man treated for non-small cell lung cancer (NSCLC) with a combination of tremelimumab and durvalumab. After treatment he developed diplopia, ptosis, fatigue, weakness, and an inflammatory myopathy affecting the extraocular muscles requiring hospitalisation. Electromyography (EMG) testing and muscle biopsy suggested inflammatory myopathy without sign of myasthenia. Within 1 month of withdrawal of cancer therapies and initiation of oral steroid therapy, ocular and systemic symptoms had resolved. This notable adverse effect has not been previously described for these drugs administered singly or in combination, and ophthalmologists should be aware of this presentation in patients treated with these agents.

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Introduction

Several novel therapeutic agents for the treatment of malignant tumours, including non-small cell lung cancer (NSCLC), have targeted immune checkpoints. These new agents have side effect profiles with autoimmune and inflammatory features that remain incompletely characterised. We report a case of drug-induced myopathy affecting the extraocular muscles in a patient being treated with a combination of tremelimumab and durvalumab for NSCLC.

Case report

A 68-year-old man presented to our eye clinic with 1 week of binocular vertical diplopia, worse on rightward gaze, as well as ptosis of the left upper eyelid. He complained of fatigue, joint pain, spasms, aches, and severe weakness in his neck, shoulders, and legs. The patient was noted to have spastic neck flexion and inability to stand from a seated position without assistance. He denied any dermatologic or gastrointestinal symptoms. His

past medical history was significant for stage IVa NSCLC status post right upper lobectomy, wedge resection of the superior segment of the right lower lobe, and hilar and mediastinal lymphadenectomy. His medical comorbidities included type 2 diabetes mellitus, coronary artery disease, remote history of skull fracture with traumatic brain injury, and benign prostatic hyperplasia. He had no past ocular history. At the time of presentation to our clinic, his NSCLC was being treated with tremelimumab 1 mg/kg and durvalumab 20 mg/kg. He had received a total of two doses of treatment, the first of which was given 1 month before symptom onset and the second 4 days before symptom onset.

The patient's best-corrected visual acuity (BCVA) at presentation was 20/20 OU with intraocular pressures of 16 and 20 mm Hg in right and left eyes, respectively. Anterior segment examination was normal with exception of 2+ nuclear sclerotic cataracts in both eyes. Fundus examination was unremarkable. Examination of the patient's extraocular movements (EOMs)

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Figure 1. Ocular motility evaluation on initial presentation. Subtle ptosis of the left upper eyelid is seen in primary gaze (center), as well as a left hypertropia seen best in rightward gaze (left) and upgaze (top).

demonstrated a left hypertropia (LHT) worse in right gaze and left upper lid ptosis (Figure 1). There was no change to the LHT with either left or right head tilt, and double Maddox rod testing failed to reveal any cyclotorsional component. The left upper lid ptosis and the LHT were not worsened by fatigue with prolonged upgaze testing and did not improve with rest. The patient was able to fuse with a 2-dioptre base-down prism held over the left eye in primary gaze.

Laboratory evaluation of the patient revealed a serum creatine kinase (CK) level elevated to 3083 U/L (reference range: 52–336 U/L) and a serum myoglobin of 2062 ng/mL (reference range: 30–90 ng/mL) in conjunction with a transaminitis on the day of his second treatment. Serum potassium measured 5.1 mEq/L and blood urea nitrogen (BUN) to creatinine ratio was elevated to 23.8. Further evaluation of the patient's new-onset complaints included rheumatologic panels negative for serum autoantibodies, including anti-3-hydroxy-3-methylglutaryl-Coenzyme A reductase (HMGCR), anti-Muscle-Specific Kinase (MuSK), and anti-acetylcholine receptor antibodies. Magnetic resonance imaging (MRI) of the orbits was unremarkable. An initial electromyography (EMG) showed normal sensory and motor nerve conduction studies, with needle electrode examination revealing complex polyphasic motor unit potentials with variable amplitude and short duration, along with a marked degree of abnormal spontaneous activity. This pattern was considered consistent with inflammatory myopathy. Repetitive nerve stimulation testing was normal without evidence of abnormal decrement at baseline, post-exercise facilitation, or post-exercise exhaustion. A muscle biopsy of the

deltoid showed infiltration of the endomysium and perimysium by CD4- and CD8-positive T cells (CD4: CD8 ratio 3:2), as well as CD20-positive B cells in the perimysium. The patient's overall clinical picture was suggestive of an inflammatory myositis, and he was started on 60 mg prednisone while holding further cancer treatments.

Over the month following symptom onset, he developed dyspnoea requiring two hospitalisations and he demonstrated a persistent leukocytosis, but his fatigue, weakness, stiffness, and body aches gradually improved. The BUN to creatinine ratio and transaminases gradually normalised. By ophthalmology follow-up examination 1 month after last treatment with tremelimumab and durvalumab, his symptoms of diplopia had resolved and ocular motility examination had normalised, with extensive alternative cover testing revealing ortho alignment in all directions of gaze (Figure 2). His CK value had fallen to 61 IU/L by 2 months following cessation of the anti-cancer regimen. Gradual taper of the prednisone was carried out over the following 6 months without recurrence of myopathy or diplopia at last follow-up, and the patient was stable from an oncologic standpoint on observation only.

Discussion

Advanced NSCLC continues to have a dismal prognosis, and there is a great need for new treatment approaches.¹ Several of these novel anti-cancer therapies have targeted immune checkpoints. Tumours employ an array of mechanisms to evade the defences of the immune system, including the promotion of regulatory T cell activity and the up-regulation of

Figure 2. Ocular motility evaluation on follow up after cessation of chemotherapeutic agents and initiation of systemic steroids. The left upper lid ptosis and left hypertropia are resolved.

genes that suppress anti-tumour T cell responses, including PD-L1 (programmed death ligand-1) and CTLA-4 (cytotoxic T-lymphocyte-associated protein 4).^{2,3}

Tremelimumab is a selective human immunoglobulin G₂ (IgG₂) monoclonal antibody (mAb) inhibitor of CTLA-4.⁴ CTLA-4 is a co-inhibitory receptor that exerts some of its effect via an interaction with CD80 and CD86 on B cells and monocytes, resulting in blockage of co-stimulation and in a reduction of interleukin-2 (IL-2) production and in T cell proliferation and activation.^{2,5} Antibody suppression of CTLA-4 may thereby cause tumour suppression by promoting T cell proliferation and activation.⁶ Monoclonal antibodies against CTLA-4 such as ipilimumab and tremelimumab have shown effectiveness against a variety of malignant tumours, including NSCLC.^{4,6}

Durvalumab (MEDI4736) is a selective human IgG1 mAb blocker of PD-L1.^{4,7} PD-L1 and PD-L2 are co-inhibitory molecules whose interaction with the PD-1 receptor on the T cell surface triggers an intracellular signalling cascade. This cascade results in inhibition of T cell proliferation, activation, cytokine production, and down-regulation of anti-apoptotic and growth-regulatory molecules such as Bcl-xL and mTOR.^{3,5} Antibody blockade of PD-L1 thereby disinhibits T cell activation and proliferation.⁴ Recent and ongoing clinical trials have attempted to exploit potential synergistic effects by directing therapy toward both of these pathways simultaneously.^{4,5,7,8}

Both of these medications work to suppress immune-evading mechanisms used by tumour cells, which generates an immune response to destroy the

tumour. Previous reports of immune-related side effects from anti-CTLA-4 monoclonal antibodies (mAbs) have commonly included dermatitis, hepatitis with transaminitis, colitis, diarrhoea, and fatigue. Rare side effects have included hair depigmentation, hypophysitis, thyroiditis, inflammatory myopathy, and lupus nephritis.^{6,9} Most of these side effects are posited to be secondary to nonspecific or cross-reactive T cell overactivity.⁹ Specific to the eye, there have been reports with these agents of decreased visual acuity, photophobia, tearing, uveitis, and episcleritis.⁹ Ocular myositis has been reported with other immune checkpoint inhibitors, including ipilimumab, pembrolizumab, and nivolumab,⁵ but no reports exist of either tremelimumab, durvalumab, or the combination of the two causing such side effect. Previous studies of combination therapy with tremelimumab and durvalumab have reported a similar profile of adverse effects compared with those of anti-CTLA-4 mAbs, and these side effects appear to be dose dependent.⁴ Additionally, there have been very rare cases of death from combination therapy due to complications of myasthenia gravis, pericardial effusion, and neuromuscular disorder.⁴ A previously reported case of ocular myositis secondary to treatment with ipilimumab presented with painful diplopia and proptosis that responded to high-dose steroids.¹⁰ The case we describe presented with painless diplopia and a lack of notable MRI findings, which differs from this previously described case of ocular myositis with a drug in this class. Given the rarity of this condition, it is possible that this case represents an atypical presentation. The possibility of systemic inflammation revealing a congenital fourth nerve palsy with spread of

comitance was considered, although we think this less likely given the absence of cyclotorsion on double Maddox rod testing, the EMG and biopsy findings, which suggested an inflammatory aetiology, and the patient's lack of any previous ocular symptoms.

We report a case of drug-induced autoimmune myositis affecting the extraocular muscles as an adverse effect of combination treatment with tremelimumab and durvalumab, the symptoms of which corresponded to the rise in CK and resolved with steroid treatment and cessation of the medications. It is not possible to say if this adverse effect was due to the combination of these agents or to one agent alone. Clinician awareness and prompt recognition of potential adverse effects is vital to limiting these outcomes and to providing safe care to patients treated with these drugs. Ophthalmologists should be aware of the potential ocular adverse effects of these drugs and should consider this in their differential diagnosis when assessing patients with diplopia, ptosis, or extraocular myopathy who are being treated with these agents.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

References

- [1] Goldstraw P, Crowley J, Chansky K, Giroux DJ, Groome PA, Rami-Porta R, Postmus PE, Rusch V, Sobin L; International Association for the Study of Lung Cancer International Staging Committee; Participating Institutions. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. *J Thorac Oncol* 2007;2:706–714.
- [2] Buchbinder E, Hodi FS. Cytotoxic T lymphocyte antigen-4 and immune checkpoint blockade. *J Clin Invest* 2015;125:3377–3383.
- [3] Mahoney KM, Freeman GJ, McDermott DF. The next immune-checkpoint inhibitors: PD-1/PD-L1 blockade in melanoma. *Clin Ther* 2015;37:764–782.
- [4] Antonia S, Goldberg SB, Balmanoukian A, Chaft JE, Sanborn RE, Gupta A, Narwal R, Steele K, Gu Y, Karakunnel JJ, Rizvi NA. Safety and antitumour activity of durvalumab plus tremelimumab in non-small-cell lung cancer: a multicentre, phase 1b study. *Lancet Oncol* 2016;17:299–308.
- [5] Barbee MS, Ogunniyi A, Horvat TZ, Dang TO. Current status and future directions of the immune checkpoint inhibitors ipilimumab, pembrolizumab, and nivolumab in oncology. *Ann Pharmacother* 2015;49:907–937.
- [6] Hunter G, Voll C, Robinson CA. Autoimmune inflammatory myopathy after treatment with ipilimumab. *Can J Neurol Sci* 2009;36:518–520.
- [7] Mok T, Schmid P, Arén O, Arrieto O, Gottfried M, Jazieh AR, Ramlau R, Timcheva K, Martin C, McIntosh S. 192TiP NEPTUNE: a global, phase 3 study of durvalumab (MEDI4736) plus tremelimumab combination therapy versus standard of care (SoC) platinum-based chemotherapy in the first-line treatment of patients (pts) with advanced or metastatic NSCLC. *J Thorac Oncol* 2016;11(4 Suppl):S140–S141.
- [8] Peters S, Antonia S, Goldberg SB, Heymach JV, Kim ES, Nakagawa K, Papadimitrakopoulou V, Mukhopadhyay P, McIntosh S, Rizvi NA. 191TiP: MYSTIC: a global, phase 3 study of durvalumab (MEDI4736) plus tremelimumab combination therapy or durvalumab monotherapy versus platinum-based chemotherapy (CT) in the first-line treatment of patients (pts) with advanced stage IV NSCLC. *J Thorac Oncol* 2016;11(4 Suppl):S139–S140.
- [9] Di Giacomo AM, Biagioli M, Maio M. The emerging toxicity profiles of anti-CTLA-4 antibodies across clinical indications. *Semin Oncol* 2010;37:499–507.
- [10] Lecouflet M, Verschoore M, Giard C, Gohier P, Le Corre Y, Milea D, Martin L. Orbital myositis associated with ipilimumab. *Ann Dermatol Venereol* 2013;140:448–451.