CASE REPORT

Ipilimumab-induced Adenohypophysitis and Orbital Apex Syndrome: Importance of Early Diagnosis and Management

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ABSTRACT

Ipilimumab is a novel anti-melanoma agent known to infrequently cause multi-organ autoimmunity. We report a case of pituitary hypophysitis and orbital inflammation followed by an orbital apex syndrome.

A 64-year-old woman with a history of skin melanoma, receiving ipilimumab treatment, was seen for near total loss of vision in the right eye and proptosis. Headache of 3-month duration preceded the onset of diplopia followed by severe loss of vision in the right eye. Neuro-ophthalmologic examination was consistent with an orbital apex syndrome. Extensive blood work and magnetic resonance imaging of the brain and orbit suggested an inflammatory process, rather than a metastatic lesion. Accordingly, the patient received high-dose methylprednisolone followed by tapering oral prednisone. At the 6-month follow-up visit, visual acuity on the right eye had significantly improved but diplopia remained, associated with large amplitude esotropia that improved incompletely though while on prednisone. The favourable outcome supported a final diagnosis of ipilimumab-induced inflammatory orbital apex syndrome and clinically silent pituitary adenohypophysitis.

The case presented herein highlights unexpected ipilimumab-associated adverse effects and proposes the possibility of an interaction between inflammatory and immune mechanisms.

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Introduction

Ipilimumab is an IgG1, immunomodulatory antibody (Ab) that targets cytotoxic T-lymphocyte-associated protein 4 (CTLA-4). It ultimately enhances the immune system action against cancerous cells. Approved by the FDA in 2011, this monoclonal Ab is effective against acute melanoma. Although ipilimumab increases the overall chance of survival, the anti-CTLA-4 Ab effect is associated with immune-related adverse events (IrAEs). These include dermatological, gastrointestinal, hepatic, endocrine, and less common ocular, renal, neurologic, and hematologic systems. There are few reports about IrAEs affecting the central nervous system and the eyes.¹

A range of neurological syndromes such as Guillain–Barre syndrome, posterior reversible encephalopathy, aseptic meningitis, hypophysitis, enteric neuropathy, transverse myelitis, chronic inflammatory demyelinating polyneuropathy, and myasthenia gravis has also been reported in the literature.¹

In a recent 2016 case-series study², among seven patients with metastatic melanoma treated with ipilimumab, four of them developed orbital inflammation, two uveitis and other IrAEs such as colitis and hypophysitis, and one had peripheral ulcerative keratitis. All were treated successfully with corticosteroids. The authors concluded that ipilimumab-associated steroid-responsive ophthalmic inflammation accompanies additional systemic IrAEs and usually improves with timely treatment.²

To our knowledge, we report the first ipilimumab-induced adenohypophysitis and orbital apex syndrome and describe clinical characteristics and outcome.

Case report

A 64-year-old Caucasian woman with a history of hypothyroidism secondary to underlying Hashimoto's thyroiditis, nontoxic multinodular

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goiter, and skin melanoma treated with ipilimumab; she developed near complete loss of vision in the right eye, preceded by diplopia and headache. The patient's protracted unilateral right-sided headache and ocular pressure initially were attributed to sinus infection. Her headache gradually worsened despite antibiotics and she developed right ptosis and diplopia. At this point, and prior to her first neuro-ophthalmology visit, computed tomography of the head/orbit was performed (Figure 1) in an outpatient setting. It excluded melanoma metastases and revealed enlarged right extraocular muscles thought initially to be consistent with thyroid eye disease. She was not treated with corticosteroid and unfortunately her right eye vision deteriorated dramatically over the course of 3 days accompanied by severe ophthalmoplegia and she was sent for evaluation to our facility.

On examination, the best corrected visual acuity was light perception in the right eye and 20/40 in the left eye. Colour vision was 0/8 in the right and 7/8 in the left eye. Pupils were equal (Figure 2B), and 4–5 mm in light and dark. A 1.8 log unit right relative afferent pupillary defect was present. Also, there was slight right eye proptosis, ptosis (Figure 2B), and ophthalmoplegia (abduction –4, supra-duction –3, and infra-duction –1). She did not have any eyelid signs of Graves, with flaccid ptosis. Fundus examination revealed slight

Figure 1. CT scan of orbit without contrast, coronal view. Asymmetric prominence of the right medial, inferior, and lateral rectus muscles compared to the left.

pallor of right nerve compared to the left, without obvious disc edema in either eye, and both eyes had small cups (cup–disc ratio 0.1). On neuro-examination, she had an absent right corneal (blink) reflex. Otherwise, neurologic exam was normal. Work-up was negative for ANA, ANCA, RPR, ACE, and IgGG4. She had elevated ESR 56 (0–20 mm/h), CRP 5.79 (<0.50 mg/dL). Thyroid function tests showed thyroid-stimulating hormone 0.031 (0.360–3.740 IU/mL), T3 1.9 (1.7–3.7 pg/mL), free T2 0.7, thyroglobulin Ab 42 (<4 IU/mL), thyroid peroxidase Ab 12 (<6 IU/mL), and thyrotropin receptor Ab 2.49 (0–1.75 IU/L). Magnetic resonance imaging (MRI) revealed mild unilateral proptosis as well as asymmetric enlargement and enhancement of the right inferior, medial, and lateral rectus muscles and the right optic nerve was compressed (Figure 2(A–C)). Interestingly, a retrospective review of MR images, 2 months prior to ocular symptoms, also showed pituitary hypophysitis (Figure 3(A–C)), which was probably clinically silent and preceded the orbital inflammation.

We discontinued ipilimumab and administered IV methylprednisolone sodium succinate (Solu-Medrol) 1 g for seven consecutive days that followed by tapering dose of prednisone at 1 mg/kg. Steroid treatment led to resolution of the headache, ocular pain, and improvement of ptosis during the second day of treatment. In view of this improvement, we reversed our initial plan for diagnostic biopsy of the extra-ocular muscles.

While on tapering steroid, the patient vision and colour perception improved gradually, albeit slowly (3 and 6-month follow-up visits). Latest visual acuity in the right eye is 20/50, corrected to 20/30 (eccentric gaze) and remained 20/20 in the left eye. The right relative afferent pupillary persisted, though. The ophthalmoplegia also improved though a large esotropia persisted with consequent diplopia after vision improvement (Figure 3(A–C)). Optical coherence tomography of the ganglion cell layers was consistent with optic atrophy (Figure 4). An attempt to stop prednisone treatment caused recurrence of several of her symptoms, including ocular pain and severe fatigue; thus, the lowest needed dose of prednisone (10 mg daily) was maintained to avoid symptom exacerbation.

Figure 2. MRI orbit with gadolinium and fat saturation shows inflammation of orbital muscles and optic nerve compression. (A) Coronal views of T2 pre-gadolinium (A) and T1 post-gad (B) sequences reveal optic nerve compression with severe inflammation and hypertrophy of ocular muscles. (B,C) MRIs of orbit with and without gadolinium and with fat saturation are compared pre-(B), post-(C) IV Solu-Medrol treatment. (B) Axial views of T1 sequences pre-, post-gad (top panels A and B consecutively) and coronal views of T2 pre-, and T1 post-gad (middle panels c and d consecutively) before treatment with high dose of IV Solu-Medrol. (C) Axial views T1 sequences pre-, post-gad (top panels E and F consecutively) and coronal views of T2 pre- and T1 post-gad (middle panels g and h consecutively) after treatment with high dose of IV Solu-Medrol. Following steroid treatment, proptosis and orbital inflammation including myositis have significantly improved. However, there is a worsening of esotropia on the right eye that likely is related to weakness of the lateral rectus. Picture of our patient is shown on admission day 1 and 3 weeks later.

Discussion

Our experience with this initially misdiagnosed case of near blindness highlights the need to increase knowledge about novel IgG1- and IgG2-isotype monoclonal antibodies used in the treatment of cancer. Timely recognition of potential complications could result in

improvement. Ipilimumab can induce a wide spectrum of neurological and ocular adverse reactions including orbital myositis and orbital apex syndrome. In our patient, the initial diagnosis of Graves' ophthalmopathy was not supported by the absence of lid lag, the severe nature of the ocular pain, and a negative thyrotropin receptor Ab. The operating mechanism(s)

Figure 3. Pituitary hypophysitis. Sagittal (top panel) and coronal (lower panel) views of T1 sequences pre-, post-gadolinium are shown 1 year before vision loss, 2 months before vision loss, and day of admission for vision loss. About 1 year before vision loss MRIs revealed a normal pituitary gland (A). Two months before vision loss, MRIs showed inflammation of the pituitary gland (B) that followed by post-inflammatory pituitary atrophy (C).

Figure 4. OCTs of nerve fibre and ganglion cell layers are shown about 3 months after the initial vision loss. Testing revealed right optic nerve atrophy as a sequelae of right orbital apex syndrome.

whereby monoclonal antibodies affect the ocular muscles is unknown. Although we favoured orbital myositis, possibly kindled by tissue deposition of ipilimumab, we did not perform a biopsy; therefore, histopathology confirmation is not available. In accordance with data published in the literature, we propose that the current chemotherapeutic agents (IgG1- and IgG2-isotype monoclonal antibodies) could lead to orbital myositis via two possible mechanisms. One mechanism could involve a direct T-cell-mediated inflammatory pathway. Alternatively, we hypothesize an additional second potential mechanism analogous to the process of IgG4-related myositis (Table 1).³ Overall, the pathogenic events that initiate IgG4-related myositis/disorders are not elucidated. Based on histopathological features from different organs, IgG4-related disease could be an antigen-driven inflammatory condition. Ipilimumab could share a common pathogenesis. A possible imbalance in T-cell types and innate immunity may be relevant to the pathogenesis of the IgG4-related disorders.⁴

The adverse effects from ipilimumab may develop as early as 2 weeks from the onset of treatment. Once IrAEs occur, permanent ipilimumab discontinuation and immunosuppression (high-dose IV steroid and/or plasmapheresis) may lead to fast improvement of ocular, neurological, and systemic reactions particularly if any life-threatening/debilitating event develops. Improvement rate varies from 1–2 weeks to a few months.

Conclusions

Recognition of the spectrum of ipilimumab side effects is critical to improve outcomes. Increased awareness of these adverse events among all physicians, but in particular oncologists, ophthalmologists, and neurologists, may decrease ipilimumab-related morbidity. In addition, knowledge of the specific mechanism that causes an overactive immune system may be applicable to severe inflammatory syndromes in different organs and may contribute to the understanding of the interactions between altered immunity, inflammation, and cancer.

Table 1. The monoclonal antibodies and their mechanism of action on the immune system.

Anticancer agent with stimulatory effect on immune system	Anticancer agent primary mechanism of action	Mechanism of action	Final mechanism of action	Hypothetical underlying pathology for orbital myositis
Ipilimumab	IgG1 isotype monoclonal antibody with inhibitory effect on CTLA-4	CTLA-4: CTLA-4 is a protein receptor that downregulate immune system by interacting with CD80, CD86 on B cells and monocytes resulting in IL-2 production and in T-cell proliferation and activation	Antibody blockade of CTLA-4 proliferates T-cell activation and proliferation	The pathology might be a T-cell-mediated myositis similar to the myositis which is seen in dermatomyositis or polymyositis
Tremelimumab	IgG2 isotype monoclonal antibody with inhibitory effect on CTLA-4			IgG4-associated orbital myositis is a well-known disease. But what about other IgG isotypes? Here, we hypothesize that IgG1 and IgG2 may cause orbital myositis
Durvalumab	IgG1 isotype monoclonal antibody with inhibitory effect on PD-L1	PD-L1: PD-L1 is an immune modulatory molecule; it binds to PD-1 receptors on T cells that inhibit T-cell proliferation, activation, cytokine production	Antibody blockade of PD-L1 thereby disinhibits T-cell activation and proliferation	IgG4-associated orbital myositis is a well-known disease. But what about other IgG isotypes? Here, we hypothesize that IgG1 and IgG2 may cause orbital myositis

Note. The hyperactivity of immune system resulting activation of different cascades or direct effect of IgG isotypes might be the underlying cause (s) of inflammation of extraocular muscles leading to orbital myositis. CTLA-4: Cytotoxic T-lymphocytes associated protein 4; IL-2: interleukin-2; PD-L1: programmed death-ligand 1.

Informed consent

Informed consent was obtained in writing from the patient for disclosure of clinical information and external photograph, for the purpose of this report.

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Declaration of interest

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

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