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Presumed Isotretinoin-Induced, Concomitant Autoimmune Thyroid Disease and Ocular Myasthenia Gravis: A Case Report

Huseyin Gursoy Idil Cakmak Nilgun Yildirim
Hikmet Basmak

Eskisehir Osmangazi University Medical Faculty, Department of Ophthalmology, Eskisehir, Turkey

Key Words
Isotretinoin · Ocular myasthenia gravis · Thyroiditis

Abstract
Introduction: There are many adverse effects that have been described for isotretinoin. To the best of our knowledge, this is the first report of a possible association of oral isotretinoin intake with autoimmune thyroiditis and ocular myasthenia gravis (OMG).
Case Presentation: A 19-year-old Caucasian male, who had used oral isotretinoin for severe acne disease for the previous six months, was referred to our clinic. He had a three-week history of diplopia and variable bilateral ptosis. Physical examination showed moderate periorbital edema and limitations of up- and down-gaze in the left eye. Laboratory findings and thyroid ultrasound were consistent with autoimmune thyroiditis. Antithyroid therapy did not relieve the clinical symptoms. Concomitant OMG was suspected. Variable ptosis and a positive response to oral prednisolone of 40 mg/day and pyridostigmine of 360 mg/day supported the diagnosis of concomitant autoimmune thyroiditis and OMG.
Conclusion: Autoimmune disorders may be triggered by oral isotretinoin treatment. Clinicians prescribing isotretinoin should be aware of the possible association between isotretinoin intake and concomitant autoimmune thyroiditis and OMG.

Introduction

Isotretinoin is a vitamin A synthetic analogue that has been widely used by dermatologists in the treatment of acne [1]. Among the many adverse effects of

Huseyin Gursoy
Camlica Mahallesi
Natura Evleri L1D2
TR–26180 Tepebasi, Eskisehir (Turkey)
E-Mail hhgursoy@hotmail.com

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isotretinoin, eye dryness, corneal and retinal abnormalities, myalgia, true myopathy, psychiatric problems, and several autoimmune disorders have been described [2–8]. A literature review has revealed very few case reports of autoimmune disorders associated with isotretinoin intake. Isotretinoin-induced inflammatory bowel disease (IBD) was the most common of these autoimmune disorders [5]. Ulcerative colitis was the diagnosis in the majority of the cases. Some of the patients developed IBD after discontinuation of isotretinoin [7], while some developed IBD during the intake of isotretinoin [5]. There is only one report of an association between isotretinoin intake and immune-mediated diabetes mellitus [6]. In this case, it was concluded that latent autoimmune diabetes mellitus could be clinically revealed after isotretinoin use. Guillain-Barré syndrome, which is an autoimmune disease of the nervous system, has been reported in two patients taking oral isotretinoin, and both cases received intravenous immunoglobulin [8]. To the best of our knowledge, this is the first reported case of isotretinoin-induced autoimmune thyroiditis and ocular myasthenia gravis (OMG) resulting from use of isotretinoin.

Case Presentation

A 19-year-old Caucasian male was referred to our clinic, with a three-week history of diplopia and variable bilateral ptosis (**fig. 1** and **fig. 2**). He had used oral isotretinoin (Roaccutane, Roche, Nutley, N.J., USA) at 1 mg/kg/day for severe acne disease, for the previous six months. No use of other medications or occurrence of any stressful events was recorded in his recent history. His complaints appeared within the last month of the successful acne treatment with isotretinoin. He first experienced a sudden onset of right eye ptosis, which recovered spontaneously within two weeks. Ptosis was worsened with fatigue. One week later, he noted left eye ptosis that was resolved within one week. Two weeks later, the right eye ptosis recurred and was accompanied by sudden onset of diplopia.

The ophthalmic, general medical and family histories for neuromuscular or autoimmune disorders were negative. He smoked 3–4 cigarettes per day. Physical examination showed moderate periorbital edema and limitations of up- and down-gaze in the left eye. Visual acuities were 10/10 in both eyes. Biomicroscopic and fundus examinations were normal.

Thyroid function tests revealed free T4 of 3.08 ng/dl (normal range 0.93–1.7 ng/dl), free T3 of 13.85 pg/ml (normal range 2.0–4.4 pg/ml) and thyroid-stimulating hormone (TSH) <0.005 mU/ml (normal range 0.27–4.2 IU/ml). The anti-thyroglobulin antibody level was normal, whereas TSH receptor antibody (TRAb) [40 U/l (normal <15 U/l)] and anti-thyroid-peroxidase antibody levels were elevated [492.2 IU/ml (normal 0–34 IU/ml)]. The creatine kinase activity and the hepatic enzyme levels were normal. The thyroid ultrasound showed moderately heterogeneous, reduced echogenicity, which was consistent with thyroiditis. Propylthiouracil (Propycil), at 200 mg/day, was prescribed by the endocrinologist. Orbital magnetic resonance imaging (MRI) and cerebral MRI indicated no pathology.

Neurological consultation was requested to exclude OMG. The acetylcholine receptor antibody test, Tensilon test, and single fiber electromyography were normal. Computerized tomography of the chest showed no evidence of thymomas. In accordance with the clinical characteristics, oral pyridostigmine (Mestinon, Valeant Pharmaceuticals, Aliso Viejo, Calif., USA) at 180 mg/day was initiated.

At the second-month follow-up, diplopia still existed, but the patient was euthyroid and ptosis had disappeared. The patient showed limitation of down-gaze in the left eye. Forced duction tests were negative in both eyes. Botulinum toxin A (Botox, Allergan, Irvine, Calif., USA), at 2.5 units, was injected into the right inferior rectus muscle.

After one month, variable ptosis recurred and diplopia persisted. In order to exclude myopathies the neurologist biopsied the left biceps brachii muscle. Ragged red fibers were seen in the samples,

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which was consistent with a mitochondrial cytopathy (MC). Pyridostigmine was stopped and oral Co-Enzyme Q10 (Co-Enzyme Q10, Life Time, Meridian, Idaho, USA) at 30 mg/day was initiated. Cardiac and neuromuscular disorders may be associated with MC, but were not detected in the patient. No clinical improvement was seen within one month; therefore, Co-Enzyme Q10 was discontinued.

Oral pyridostigmine at 360 mg/day and oral prednisolone (Deltacortril, Pfizer, New York, N.Y., USA) at 40 mg/day were initiated to treat the concomitant autoimmune thyroiditis and OMG. The clinical symptoms improved completely within one week.

Discussion

Regarding the patient presented in this case report, there is a possible relationship between isotretinoin intake and concomitant autoimmune thyroiditis and OMG. The clinical symptoms did not reverse upon completion of the acne treatment, since the autoimmune reactions had already been triggered. It is reported that isotretinoin has immunomodulating effects that may induce some autoimmune diseases such as Crohn's disease, immune-mediated diabetes, and Guillain-Barré syndrome [5–9].

Genetic predisposition and a variety of environmental factors have been found to influence the development of autoimmune diseases [10]. Drugs are one of the important environmental factors, which may be the trigger factor for the development of autoimmune diseases in genetically predisposed people [10]. It has been shown that isotretinoin is involved in induction of apoptosis, activation of T cells and B cells [9, 11, 12]. In our case, it is unclear how isotretinoin caused the development of autoimmune thyroiditis and OMG, but it is possible to suggest that isotretinoin triggered autoimmunity through its immunomodulating effects [9, 11, 12].

Most screening tests for mitochondrial cytopathy are not sensitive, and in this case report, the observed ragged red fibers probably led to a false positive diagnosis [13]. The clinical and laboratory findings and the response to combined pyridostigmine and steroid treatment were consistent with concomitant autoimmune thyroiditis and OMG. The laboratory and thyroid ultrasound findings and moderate periorbital edema suggested thyroid eye disease (TED). Graves' disease was the most likely etiology for the current TED, because TSH receptor antibody was elevated in addition to hormone levels, indicating hyperthyroidism [14]. Propylthiouracil was initiated accordingly. The patient was euthyroid at the next visit, but still complained of diplopia.

Periorbital swelling, eyelid retraction, proptosis, and restrictive and congestive ocular myopathy are common signs of TED [15]. In the present case, periorbital edema and laboratory findings supported TED. Diplopia, due to involvement of extraocular muscles, was a persistent finding and did not resolve until combined high-dose oral pyridostigmine and prednisolone was initiated. Diplopia could also be a consequence of autoimmune thyroiditis. However, normal orbital MRI and negative forced duction tests did not support a diagnosis of Graves' ocular myopathy [15]. However, ptosis, which is not a feature of TED, was one of the presenting signs in the present case [15]. The spontaneous recovery of the ptosis at the second-month follow-up and the following recurrences of the ptosis were most likely due to the fluctuating nature of OMG.

The diagnostic and laboratory tests for OMG were negative. However, it has been reported that these tests may be negative in some OMG cases [16]. In the current case,

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the variable ptosis, the limitations of eye movements, and response to pyridostigmine were used to determine the diagnosis of OMG [16]. Steroids may be effective in both TED and OMG, supporting concomitant diagnosis of both diseases [17]. Epidemiological studies report that autoimmune thyroiditis occurs in 5–10% of OMG patients [18]. Although oral steroid and pyridostigmine relieved the symptoms, thyroid hormone levels must be checked during the follow-up. It is well known that diagnosis of OMG is a challenging process. Although a clinical diagnosis may be confirmed by laboratory testing, clinical findings of fluctuating and fatigable weakness leading to ptosis and diplopia are the most important elements of diagnosis [19]. In the present case, the emphasis was solely on TED, because of negative test results for OMG. This delayed the correct diagnosis. The entire clinical findings could not be explained by autoimmune thyroiditis. Variable ptosis and involvement of the extraocular muscles without any enlarged muscles, as observed by orbital MRI, supported the diagnosis of concomitant autoimmune thyroiditis and OMG [19].

Conclusions

A case is reported of possible association between isotretinoin intake and autoimmune disorders. Autoimmune reactions may be triggered by oral isotretinoin treatment. Patients with acne should be assessed for autoimmune disorders or any predisposition to their development prior to treatment. Clinicians prescribing isotretinoin should be aware of the possible association between isotretinoin intake and concomitant autoimmune thyroiditis and OMG.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Disclosure Statement

The authors declare that they have no financial conflict or competing interest.

Fig. 1. Limitation of up-gaze in the left eye at the first visit.

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Fig. 2. Right ptosis at the first visit. Isotretinoin, thyroiditis and myasthenia gravis.

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