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Single Case

Pseudotumor of the Larynx: A Previously Unreported Side Effect of Apremilast

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Keywords
Laryngeal pseudotumor · Laryngeal obstruction · Side effect · Apremilast

Abstract
Apremilast (Otezla®) is a relatively novel orally administered non-biologic disease-modifying anti-rheumatic drug (DMARD) extensively used in the management of psoriasis and psoriasis arthritis, lately approved for treating oral ulcerations in Behçets disease. Its advantageous side effect profile together with its uncomplicated follow-up and monitoring when compared to other DMARDs facilitates even a broad off-label prescribing. Here, the first case of laryngeal pseudotumor in a patient treated with apremilast for plaque psoriasis is presented.

Introduction

Apremilast (Otezla®) is an orally administered phosphodiesterase 4 inhibitor. Phosphodiesterase 4 is an enzyme involved in degrading cAMP, thereby stimulating the production of pre-inflammatory mediators and suppressing the anti-inflammatory response [1]. Apremilast is widely used in psoriasis and psoriasis arthritis reducing inflammation, thus eliminating cutaneous manifestations and improving joint functionality, lately approved for treating oral ulcerations in Behçets disease [1–3]. Considering that it is generally well tolerated by the

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patients, apremilast is also used in other inflammatory conditions when conventional treatment induces too many side effects, proves to be unsuccessful or the patient is not eligible for other available drugs [3, 4]. Alopecia areata, atopic dermatitis, hidradenitis suppurativa, cutaneous sarcoidosis and discoid lupus are examples of off-label prescribing [2, 5–7].

Apremilast is a relatively novel non-biologic disease modifying anti-rheumatic drug (DMARD) with an advantageous safety: when compared to other DMARDs, apremilast has a favourable side effect profile, is not contraindicated for use in women in fertile age [3], exhibits a good profile of efficacy and safety even among elderly patients [8] and is linked with lower risk for myocardial infarction and stroke among other approved psoriasis treatments [9]. No other monitoring is required apart from weight controls, a follow-up of neuropsychiatric adverse events or the commonly self-limited gastrointestinal symptoms when compared to other non-biologic DMARDs such as methotrexate (i.e., liver toxicity, interstitial lung disease, bone marrow suppression) and cyclosporine (i.e., renal toxicity) [10]. Furthermore, monitoring therapy in biologic DMARDs (e.g., inflixaimab) is rather demanding when considering inter alia elevated risk for establishing malignancy, autoimmunity, heart failure and severe infections due to neutropenia [10].

We present a rare complication in a 74-year-old female patient with severe plaque psoriasis treated with apremilast.

Case Report

With a medical history of hypertension, atrial fibrillation, and spirometry findings of chronic obstructive pulmonary disease, although a nonsmoker, the patient was diagnosed with extensive plaque psoriasis 10 years ago. She was initially treated with UVB phototherapy, however with a rapid relapse of the cutaneous plaques and severe pruritus. A subsequent treatment attempt with methotrexate resulted in liver toxicity despite the successful elimination of the plaques and the pruritus. The patient continued with dense phototherapy sessions until October 2017 when exacerbated symptoms, mainly severe pruritus prompted a reassessment of the treatment strategy. Considering the patient's age and cardiovascular comorbidities, treatment with biological agents (e.g., infliximab) was assessed by the dermatologist as inappropriate, thus a standard dose of apremilast (60 mg twice a day) was prescribed. Except for severe transient diarrhea and a slight abdominal pain during the first 2 weeks, the treatment was well tolerated by the patient with a near-complete resolution of the psoriasis lesions.

The patient was referred to the Otolaryngology Department in October 2018 with a 3-month history of dysphagia, unilateral odynophagia and dyspnea. An oral contrast swallow examination had shown an expansive lesion in the right side of the hypopharynx. The clinical examination revealed a supraglottic submucosal mass without mucosal engagement, under the right aryepiglottic fold, extending posteriorly to hypopharynx, medially to false vocal cord and laterally to the lateral wall of the pharynx displacing epiglottis to the left side (Fig. 1a). The laryngeal vestibulum was partially occluded thus causing a mild inspiratory stridor. The only slightly abnormal values within the extensive laboratory test performed were C-reactive protein (13 mg/L, reference <4 mg/mL) and white blood cell count (10.0 $\times 10^9$/L, reference interval: 3.5–8.8 $\times 10^9$/L). Further investigation with computed tomography showed a 2.5-cm mass arising from the lateral wall of the pharynx, loading contrast irregularly, suggesting a possibly malignant tumor (Fig. 1b, c).

Core needle biopsy from the lesion under general anesthesia showed fibrosis with chronic nonspecific inflammation and hyperplastic squamous epithelial fragments. A second suspension laryngoscopy was performed to obtain more representative specimens for pathology assessment. Despite the combination of CO_2 laser dissection together with cold instruments, it was impossible to reveal a demarcated mass; however, deep cold forceps biopsies were obtained. Because of the progress of the expansive lesion within a few days and the risk for a compromised airway due to an unstable aryepiglottic fold with a tilting right arytenoid cartilage in the laryngeal vestibule, a tracheostomy was performed concurrently. Again, the biopsies were not conclusive, showing unspecific acute and chronic inflammation with fibrosis. Complementary pathological examination showed no signs of vasculitis, IgG4-related disease or amyloidosis. In a parallel immunological workup including ANA, ANCA, anti-CCP, a marginal increase in ANA was found not regarded though as diagnostic. Apremilast medication was discontinued in December 2018 following a suspicion that the pseudotumor could be a side effect of the treatment.

In January 2019, the patient presented to the Emergency Department due to dislodgement of the tracheostomy tube. Laryngoscopy revealed a substantial reduction of the pseudotumor (Fig. 2) allowing for safe decannulation. Subsequent follow-up showed an almost complete remission of the pseudotumor, both clinically and radiologically (Fig. 3). The patient recovered almost completely after 6 months having just a mild functional dysphonia. This previously unknown side effect was reported to the Swedish Medical Products Agency.

Discussion

With only a few mild to moderate adverse events reported, apremilast is a safe and effective approved medication in patients with psoriasis, psoriasis arthritis and Behçet's disease. Discontinuation of treatment due to common side effects is rare [5]. According to Langley and Beecker [5], diarrhea and nausea are frequently mild and self-resolving within 1 month, headache could be handled with conventional painkillers, whereas nasopharyngitis is not a reason for treatment termination and is regularly managed with nasal irrigation, antihistamines and antibiotics upon culture-proven bacterial infection [5]. A PubMed search identified several previously reported unusual side effects of apremilast such as severe bitter taste, chronic diarrhea with malnutrition, cutaneous hyperpigmentation, chronic tearing, recurrence of melanoma and purpura annularis telangiectodes of Majocchi [11–16]. An association with an elevated suicidality risk was also found during the clinical trials [17].

To our knowledge, this is the first reported case identifying a pseudotumor of the larynx associated with apremilast treatment leading to a potentially life-threatening, severely compromised airway. When the medication was discontinued the pseudotumor had a complete remission.

In conclusion, the process of a broad-minded medication review is always of importance to assess potential interactions or adverse events in patients presenting with signs or symptoms of unclear cause.

Statement of Ethics

The authors have no ethical conflicts to disclose. The patient has given written informed consent to publish this case (including publication of images). The study has been done according to the Declaration of Helsinki.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for the manuscript, take responsibility for the integrity of the work as a whole, and gave final approval to the version to be published.

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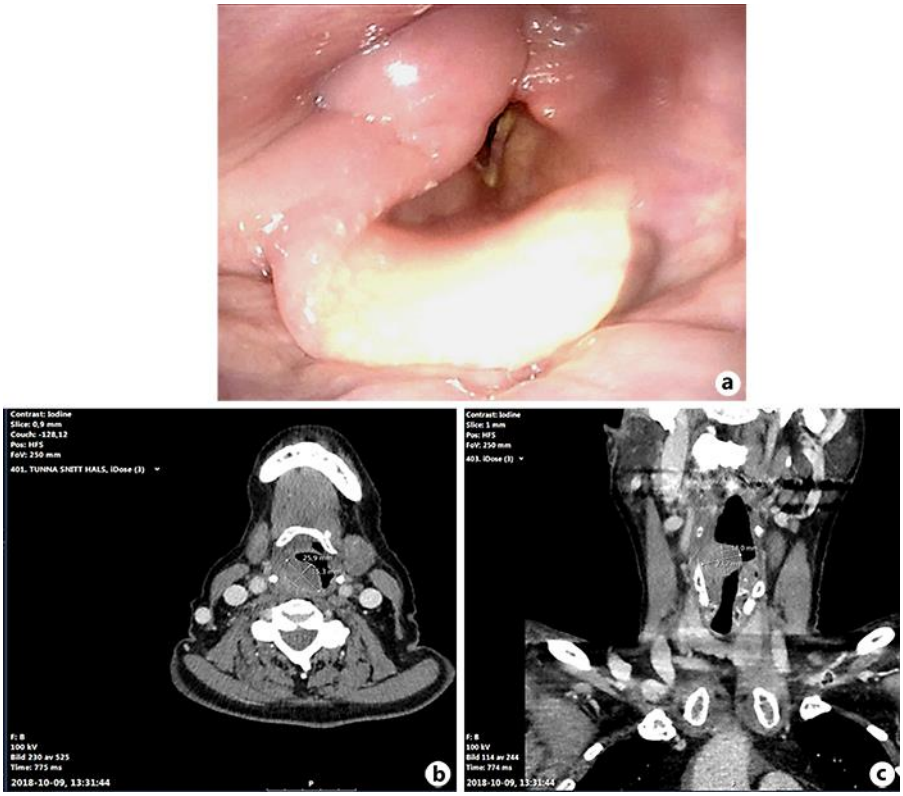

Fig. 1. Supraglottic submucosal mass on the right side of the larynx, inferior to the right aryepiglottic fold and piriform sinus, October 2018. **a** Flexible video laryngoscopy. **b** Axial computed tomography scan of the neck. **c** Coronal computed tomography scan of the neck.

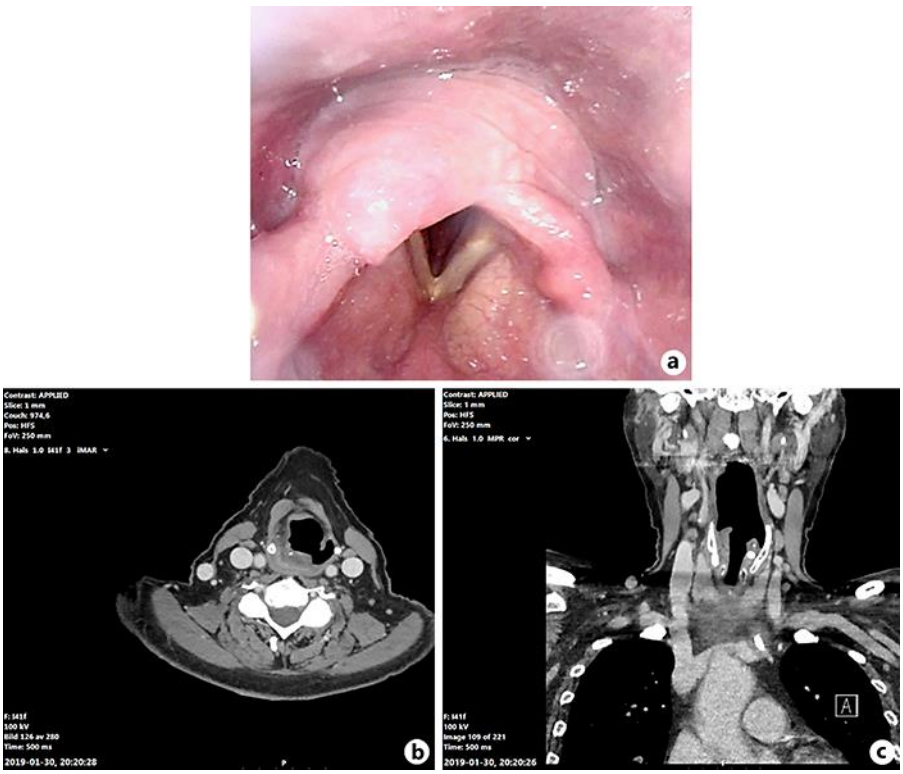

Fig. 2. Substantial regress of the pseudotumor within 1.5 months after discontinuation of apremilast, January 2019. **a** Flexible video laryngoscopy. **b** Axial computed tomography scan of the neck. **c** Coronal computed tomography scan of the neck.

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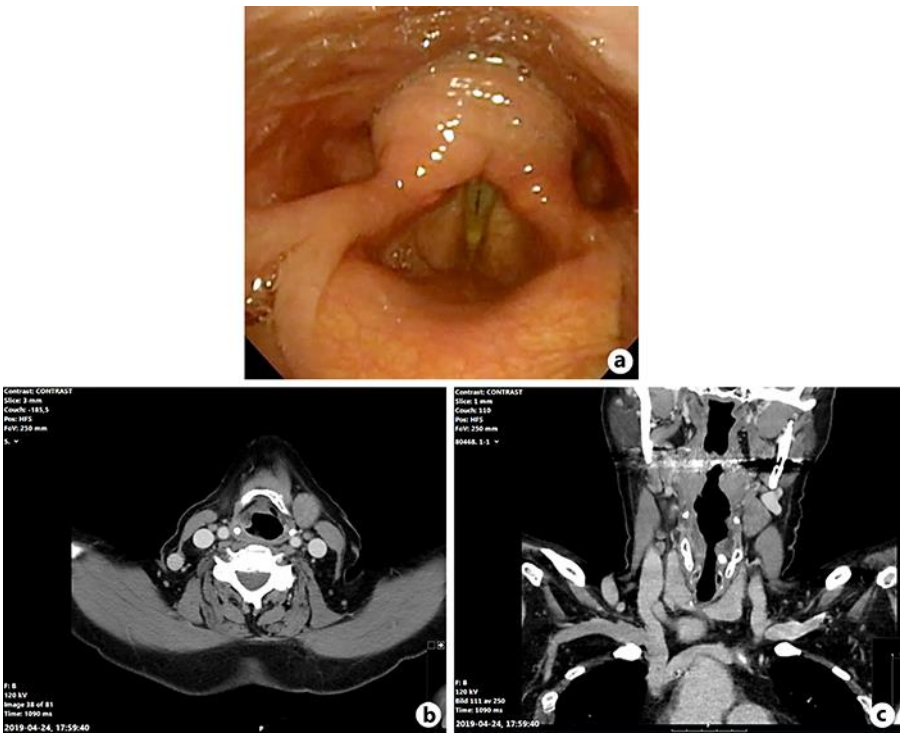

Fig. 3. Complete regress 4 months after the discontinuation of apremilast, April 2019. **a** Flexible video laryngoscopy. **b** Axial computed tomography scan of the neck. **c** Coronal computed tomography scan of the neck.