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Case Presentation

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# Dupilumab-Associated, Long-Lasting, Late-Onset, Large Local Reaction at the Injection Site in a Patient Treated for T2 Severe Asthma: A Case Report

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## Abstract

We present the case of a 47-year-old male who underwent treatment with Dupilumab 300 mg every two weeks who developed after six months' treatment a rare cutaneous reaction such as a long-lasting cutaneous reaction at the site of dupilumab subcutaneous injection together with eosinophilia; the patient has been switched, after a 2-month wash out period, to benralizumab 30 mg since without developing adverse reactions.

## Introduction

Dupilumab is a monoclonal antibody that targets both IL-4 and IL-13 signaling approved for atopic dermatitis, Type 2 (T2) inflammation driven asthma and Chronic Rhinosinusitis with Nasal Polyps (CRSwNP). In pre-marketing phase, injection-site reactions were the most reported side effects (adult, 6% to 18%; adult and pediatric, 38%), especially at their initial dose. During post-marketing surveillance, there have been several reported cases of adverse dermatologic reactions, including facial and neck erythema **[1].** Furthermore, few cases of generalized urticaria, rash, erythema nodosum, erythema multiforme were detected. Dermatologic side effects were more frequently observed (e.g., of new-onset or worsening psoriasis, alopecia areata) in patients treated with dupilumab for atopic dermatitis [2], but there is

limited knowledge about these and other dermatological effects, particularly in patients with T2 asthma. Here we present the case of a 47-year-old male who underwent treatment with Dupilumab 300 mg every two weeks (after a bolus of 600 mg at beginning of treatment) who developed after six months' treatment a long-lasting cutaneous reaction at the site of dupilumab subcutaneous injection together with hyper-eosinophilia; the patient has been switched, after a 2-month wash out period, to benralizumab 30 mg since November 2022 without developing adverse reactions.

## Case Presentation

We report the case of a 47-year-old male patient with a history of Chronic Rhinosinusitis (CRS) and asthma when he was seventeen years-old treated with Inhalant Corticosteroids (ICS). At the age of 40 he began to manifest dyspnea despite ICS treatment and therefore was prescribed a combination treatment with high dose inhaled corticosteroids and long-acting beta 2-agonists (ICS/LABA), hypertonic saline nasal spray and topical corticosteroids at need together with once daily cetirizine 10 mg tablets to relieve his nasal symptoms.In the same period after an ENT investigation, Chronic Rhinosinusitis with Nasal Polyps (CRSwNP) was diagnosed and underwent nasal polyps' surgery. At the age of 45, despite maximal inhalant asthma treatment he presented frequent dyspnea episodes and needed short courses of OCS treatment with prednisone 5 mg daily. However, after OCS treatment he presented worsening of dyspnea and CRS symptoms and decided to attend the Allergy and Clinical Immunology Unit asthma center at our hospital. The Asthma Control Test (ACT) score was 16 and pulmonary function tests showed a Forced Expiratory Volume in one second ($FEV_1$) of 62% (2.42 L) and Absolute Eosinophil Count (AEC) of 500/$mm^3$; therefore, a clinical diagnosis of severe eosinophilic asthma was made and biological therapy with dupilumab was started. The standard recommended dosage regimen for severe asthma associated with CRSwNP was used i.e. a 600 mg bolus of subcutaneous Dupilmub was adminstered in the outpatient unit followed by Dupilumab 300 mg every two weeks which was auto-injected by the patient at home after being trained to do so. Dupilumab 300 mg subcutaneously maintenance treatment was continued for 28 weeks, from March to August 2022; on the 30 of August, 12 hours after a scheduled auto injection of 300 mg dupilumab 300 mg dupilumab subcutaneously, the patient developed a delayed injection-site reaction without itching or burning sensation.

The patient did not worry about it as any other cutaneous lesions were present in the rest of the body. Two week later, on 15 of September, he proceeded auto injecting the scheduled dose of 300 mg Dupilumab on the opposite side of the abdomen, but about 10 hours later he developed a cutaneous reaction like the previous one.

Before continuing treatment with Dupilumab two weeks after, as the lesions had not disappeared, he came to the clinic to show the lesions. A reddish oval erythematous lesion of the diameter of 12 cm in width and 5 cm in length was present in the left part of the abdomen below the waist and around 5 cm from the umbilicus **(Figure 1).** On the other side of the abdomen a residual local erythematous lesion was still visible at the prior auto injection site of a scheduled 300 mg dupilumab 4 weeks before **(Figure 2).**

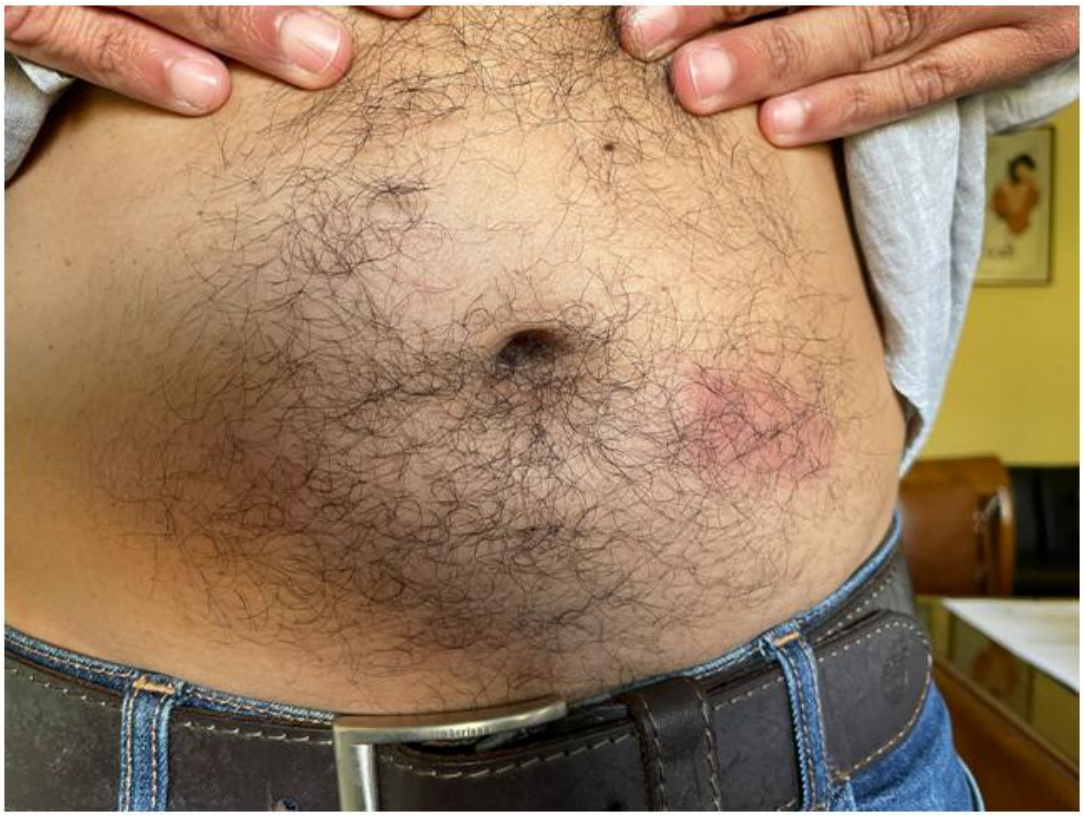

**Figure 1:** Reddish oval erythematous lesion on the patient's **left side** of the abdomen as a sequela of the delayed skin reaction appeared after an auto injection of 300 mg of Dupilumab two weeks before.

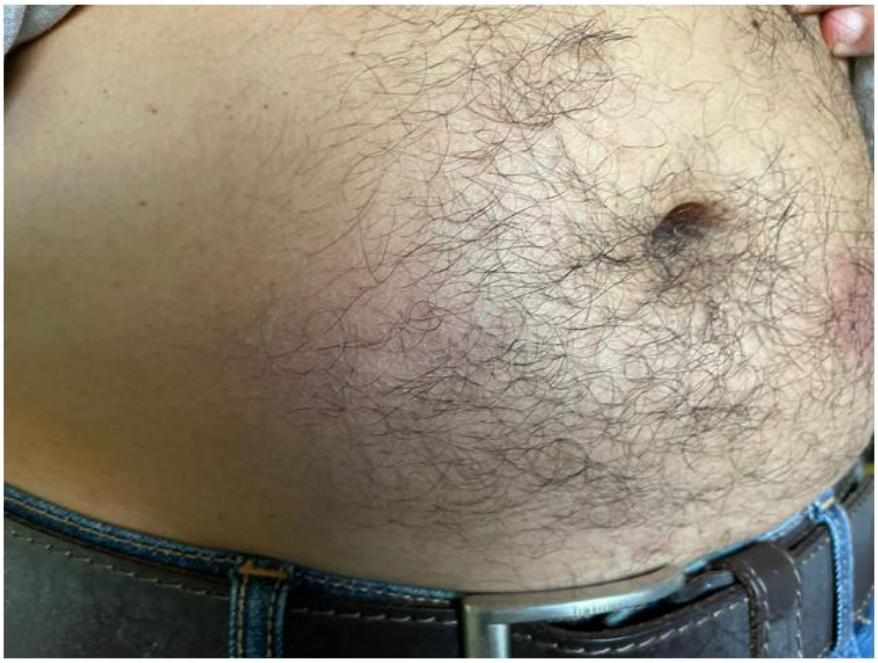

**Figure 2:** Residual local erythematous lesion at the prior injection site, still visible 4 weeks after, and, on the opposite side of the abdomen, the new lesion appeared 2 weeks after a following scheduled subcutaneous dupilumab auto injection.

The cutaneous lesions resolved spontaneously without any sequelae within 30 days from their appearance. A full blood count showed hypereosinophilia with an AEC of 830/mmc$^3$, therefore higher than when Dupilumab had been started. Any other concurrent systemic symptom occurred. The patient had a negative history for pre-existing skin disorders, non-steroidal anti-inflammatory drug sensitivity and allergies. Skin prick tests for the most common inhalant allergens were negative and total IgE levels 47 kU/L, were within normal ranges. After two months wash-out from Dupilumab therapy, Benralizumab an anti-IL5 receptor treatment was started and is still ongoing. No cutaneous reactions have appeared in the injection site, up to now, and AEC is of 0 eosinophils/mmc$^3$ and severe eosinophilic asthma is controlled. Informed consent was obtained from the patient to publish the case report along with all accompanying visual elements.

## Discussion

Dupilumab is generally well tolerated and is an effective therapy for patients with severe asthma. The dupilumab package insert reports, apart from other hypersensitivity symptoms like anaphylactic reaction and angioedema, temporary injection-site disorders and facial rash among dermatologic reactions. Specifically, early onset, dose dependent injection-site reactions have been documented with dupilumab in pre and post-marketing phases **[3].** Typical injection site reactions occur most often with initial loading dose and resolve within 48 hours of injection. However, in our case the time to onset and the recovery period are not coherent with the most commonly observed local reactions following dupilumab administration. Our patient developed a previously unreported localized reaction 28 weeks after receiving therapy uneventfully.The timing and the atypical examination findings of the reaction suggest cell-mediated immunity associated with delayed-type hypersensitivity reaction. These observations are consistent with a recently published case report of a delayed hyperpigmented injection-site reaction occurring approximately one year after chronic dupilumab use **[4].** Analogously to our patient, the lesions persisted for four to six weeks before resolving spontaneously.Other few examples of dupilumab-related delayed localized reactions have been published **[5,6].** Interestingly, all published cases about delayed adverse reactions refer to dupilumab use in patients with asthma and/or rhinosinusitis with nasal polyposis, type 2 inflammation conditions, differently from other typical dermatological reactions that more frequently appear when dupilumab is used in patients with atopic dermatitis. Delayed-type hypersensitivity reaction, which is a T-cell-mediated reaction depending on both CD4+ and/or CD8+, cannot be excluded as a possible reason for our reported reaction.

Our patient exhibited concomitantly eosinophilia that may also be correlated to dupilumab and that completely resolved after treatment cessation. Transient eosinophilia (AEC ≥ 500/mmc), commonly reported with dupilumab, could be also associated with an augmented risk of worsening of pre-existing hypereosinophilia symptoms **[7,8]** or lead to new-onset adverse events **[9].** From literature data, a maximum increase in blood eosinophils usually occur at approximately 16-20 weeks after starting therapy **[10].** In our patient, the delayed injection site reaction was self-limited without long-term sequelae with the improvement of symptoms after discontinuing dupilumab treatment. The temporal relationship, the duration and the pattern of the adverse effect indicated a different mechanism from common local reactions. Such local reactions at the injection site were not detected in other patients in our clinic. It's not clear if this atypical local reaction could be correlated to the higher eosinophil count induced by dupilumab treatment even if hypereosinophilia without cutaneous lesions is reported to occur frequently in patients treated with dupilumab.What is peculiar in our case is that hypereosinophilia occurred 28 weeks after starting dupilumab treatment while usually it is reported to occur earlier after

starting treatment; it cannot be ruled out that possible migration of blood eosinophils to dupilumab injection-site took place [3]. Such reactions could be considered rare but should not be undervalued.After applying Naranjo's algorithm for causality assessment in our case, the resulting score was probable.

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