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Case Report

Patient on allergen immunotherapy developed systemic lupus erythematosus?– A clinico-pharmacological look out

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ABSTRACT

Drug induced lupus is an autoimmune condition secondary to drug exposure which leads to development of systemic lupus erythematosus (SLE). However, labelling the culprit drug needs a prudent insight into the pharmacological plausibility of each of the offending drugs in suspicion. Here we present a report where allergen immunotherapy was suspected to cause SLE and a deeper clinico-pharmacological evaluation cleared the air.

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1. Introduction

Allergen Immunotherapy (AIT) has seen widespread advancements in the arena of atopic diseases over the past decades. However, its use has been linked and has regarded contraindicated in patients with rheumatologic complications. Evidence to support the idea that AIT can trigger autoimmune disease is considerably weak and is mainly based on few case reports highlighting causation of vasculitis.¹ However, no report of patients developing autoimmune diseases has been reported from randomised controlled trials probing the effect of AIT. Even, there exist pharmaco-epidemiological studies which have failed to detect any increased risk of autoimmune disease development during AIT compared with other conventional allergy procedures.

Nevertheless, due to lack of available data, researchers propose there is relative contraindication in autoimmune

disorders in remission and absolute contraindications in active forms with AIT. As a principle of caution, it is prudent to undergo a detailed risk-benefit assessment in auto-immune disease candidates in need of AIT. A detailed clinical examination of the patient status along with careful consideration of all related factors may show up the flip side of the story. Here we present a similar instance of clinical dilemma in a 24-year-old male.

2. Case Report

MK, 24 year old male, patient initially presented with moderate to severe persistent allergic rhinitis for 1 year and asthma for 2 years on step 3 management strategy. His initial laboratory work-up demonstrated eosinophilia (14%) in peripheral blood smear with total leucocyte count (7800/uL), elevated IgE total (2045 IU/ml), high FeNO (78 ppb). Skin prick test report suggested hypersensitivity with dust mites, pollens like *Cocos nucifera*, *Azadirachta indica* and *Cynodon dactylon*. He had also skin prick test positivity with foods like milk, wheat, cauliflower, prawn,

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hilsa and egg. Spirometry report conferred obstructive ventilatory pattern with 18% reversibility and 292 ml improvement in FEV1 after salbutamol inhalation. Patient had a childhood history of maculopapular rashes with severe itching over flexural aspects of both upper limbs from his infancy; however, it subsided by 6 years of age and was treated by dermatologists with different antihistamines and topical steroid and emollient. With a diagnosis of asthma and moderate to severe persistent allergic rhinitis pharmacotherapy with metered dose inhaler (MDI) budesonide 400 mcg plus formoterol 6 mcg fixed dose combination 2 puffs twice daily via spacer, fluticasone furoate nasal spray 1 spray in both nostrils twice daily and montelukast 10mg and fexofenadine 120 mg fixed dose combination were initiated at a dedicated allergy clinic on november, 2016. He was co-prescribed with allergen immunotherapy with Dermatophagoides pteronyssinus 50% and Dermatophagoides farina 50% composition. He responded well to this pharmacotherapy and allergen immunotherapy. After 1 year of treatment initiation, he needed SOS use of nasal spray along with budesonide 200 mcg plus formoterol 6 mcg fixed dose combination 1 puff twice daily via spacer. After 3 years of initiation of allergen immunotherapy, at around December 2019 he required only SOS use of MDI. He was diagnosed with psoriasis on January, 2019 and treated by dermatologist, was controlled with topical steroid and emollient.

In January 2020 he had presented to the allergy clinic with fever for 2 weeks and bilateral pleural effusion for which he was advised hospital admission. Under the supervision of rheumatology and chest medicine specialists he was treated after being diagnosed with SLE. The case was then referred for clinical pharmacological consultation for better understanding regarding the causality of this 'suspected case of AIT induced SLE'. After detailed history taking, clinical examination and evaluation of laboratory results it was found to be 'Unlikely' with allergen immunotherapy as per WHO-UMC scale and 'Doubtful' as per the Naranjo Causality assessment scale.

3. Discussion

The application of AIT in patients with autoimmune disease is controversial. Drug induced lupus (DIL) is an autoimmune condition where SLE like features appear after administration of culprit drug. Procainamide and hydralazine are associated with the highest incidence DIL, All anti-TNF agents have been associated with DIL, with the risk being higher with etanercept and infliximab carry higher risk to develop DIL among all anti TNF alpha agents.^{2,3} There are a few numbers of drugs which have definite causal relationship with DIL like interferon-alpha, minocycline, isoniazid, rifampin, phenytoin, penicillamine, quinidine, phenytoin, methyldopa, chlorpromazine, carbamazepine, ethosuximide, propylthiouracil, and

sulfasalazine. A few case series and case reports are suggesting that drugs like statins, ACE-inhibitors, pantoprazole, omeprazole, gold salts, non-steroidal anti-inflammatory agents (NSAIDs), oral contraceptives and herbal medications (alfalfa sprouts, echinacea, and melatonin) have possible causality with DIL.⁴ In this case patient presented with SLE after 3 years 2 months of initiation of AIT. Drug induced lupus may appear after few weeks to months of offending medication introduction, 3 years lag period is quite high in this regard. After de-challenging AIT for more than 1-year SLE like features are persisting and patient require specific therapy for SLE to control flare up. DIL is generally reversible. After withdrawing offending drug symptoms disappear within weeks to months. One of the proposed mechanisms of DIL is inhibition of Th1 response by anti TNF alpha agents which increase Th2 response and lead to generation of autoantibodies.⁵ In case of AIT there is an opposite situation. By virtue of AIT there would be high Th1 response and decrease in Th2 response and pharmacological plausibility is not explaining this reaction.

Allergen immunotherapy should be used with caution when benefits outweigh potential risks in an individual patient in case of patient with systemic autoimmune disease.⁶ Impaired balance of T-helper-cell (TH) subsets (TH1/TH2/TH17) and regulatory T-cells (Tregs) is contributing to the pathophysiology of Systemic lupus erythematosus (SLE). One study had demonstrated reduction in IFN- γ (marker of TH1 activity) and TGF- β 1 (marker of Treg activity) with the elevation in IL-6 and IL-17 (marker of TH17). Derangement of TH17/Treg balance in blood would be responsible for development of SLE. This causes an increased pro-inflammatory response especially in the active form of the disease.⁷ Allergen immunotherapy causes reduction in the production of histamine releasing factors from mononuclear cells⁸ and had decreased immediate and late-phase allergen challenged nasal reactions. Eosinophil counts in nasal secretions after nasal challenge was decreased in allergen immunotherapy treated groups.^{9,10} There is decrement in allergen-specific CD4 + cell proliferation and changes of cytokines produced by T-cell at local allergen challenge sites by allergen immunotherapy. Following allergen immunotherapy there would be upregulation of T-helper (Th) 1 CD4 + cell-type cytokines (interferon gamma, IL-2) without any effect on CD4 + cell Th2 cytokine (IL-4, IL-5) expression.^{11,12} Regulatory T (Treg) cells and related cytokines like IL-10 and transforming growth factor beta suppress Th2-type immune responses. This would control allergic diseases. Acting on B cells Treg cells increase IgG4 and IgA and decrease IgE. There would be decrease in release of proinflammatory cytokine from mast cells, eosinophils. Allergen induced lymphoproliferative responses have been decreased after immunotherapy. Allergen specific immune

deviation from a Th2 to a Th1 is the key mechanism by which allergen immunotherapy works.¹³ There are no studies which suggest increase in Th17 responses by allergen immunotherapy. It is not right to state allergen immunotherapy has causal relationship with development of SLE.

4. Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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