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A case report

Allergen Injection Immunotherapy for Seasonal Allergic Rhino-Conjunctivitis with Co-morbid Asthma: A case report

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العلاج المناعي لحساسية الأنف الموسمية وإلتهاب الملتحمة مع الربو: تقرير حالة

الملخص
بالرغم من ثبوت ارتباط في الاعتلال الوظيفي بين حساسية الأنف والملتحمة والربو ، إلا أن الدراسات السريرية في علاج هذه الامراض باستخدام حقن العلاج المناعي ليست كافيه. والدراسة الحالية هي حالة انثى سعوديه عمرها 33 سنة لديها نوبات من العطس واحتقان وسيلان الأنف، وتستيل أنفي خلفي، مع حكة في العينين منذ سن 18 عاما، مع تكرار هذه الأعراض فى أوائل الربيع ومواسم الصيف. وقد ازدادت هذه الأعراض سوءا تدريجيا مع اضطراب في أداء العمل والنوم والأنشطة اليومية. وكان اختبار وخز الجلد لمسببات الحساسية المستنشقه الشائعه لهذه المريضه ايجابيا وخصوصا طلع شجرة المسكيت. وقد أكدت الأعراض الموسمية والنتائج السريرية واختبار الحساسية تشخيص حساسية الأنف الموسمية والتهاب الملتحمة مع الربو كما يلي: كانت المريضه تستفيد جزئيا لمضادات الهيستامين والكورتيزون المستنشق، علاوة على ذلك تلقت المريضه دورات متكررة من الكورتيزون عن طريق الفم للسيطرة على الربو خلال التفاقم ، وأخيرا،فقد لاحظت المريضة تحسنا كبيرا فى أعراض الحساسية المزعجة ونوعية الحياة بعد بدء العلاج المناعي.

ABSTRACT

A pathophysiologic connection between allergic rhinitis, rhino-conjunctivitis, and asthma has been proposed. However, there are insufficient clinical studies of Allergen Injection Immunotherapy on these comorbid conditions. This is a case study on 33-year-old Saudi female experiencing episodes of sneezing, nasal congestion, runny nose, and post-nasal drip with itchy watery eyes, since the age of 18 years that occur frequently in early spring and summer seasons. Her symptoms have been progressively worsening in severity with significant disruption in work performance, sleep, and daily activities. In vivo skin prick testing to common inhalant allergens was positive mainly to Prosopis Juliflora (mesquite) pollens. Seasonality of symptoms, clinical findings, and allergy testing have established the diagnosis of seasonal allergic rhino-conjunctivitis with comorbid asthma as follows: the patient had partial benefit to antihistamines and inhaled steroids; moreover, the patient received repeated courses of oral steroids to control asthma exacerbations; finally, the patient noticed alleviation of troublesome allergy symptoms and dramatic improvement in quality of life after commencing immunotherapy.

INTRODUCTION

Seasonal allergic rhinitis (SAR), also known as hay fever, is an inflammatory condition of the upper airways that occurs in response to exposure to airborne allergens (typically tree, grass, and weed pollens) in sensitized individuals. SAR is distinguished from perennial allergic rhinitis (PAR), which is triggered by continuous exposure to house dust mites, animal dander, and other allergens generally found in an individual's indoor environment. Patients may have either SAR, PAR, or both (i.e., PAR with seasonal exacerbations).

In recent times, the incidence of allergic diseases, particularly allergic rhinitis (AR), has been increasing worldwide. It affects approximately 30 percent of adults and up to 40 percent of children in industrialized societies.[1] In developing countries, the International Study of Asthma and Allergies in Childhood (ISAAC) showed that 50% of adolescents are affected.[2] It is estimated the minimum prevalence of AR to be 8.8 percent in the United States[3], and 24 percent in UK population[4], while the reported prevalence in Saudi population is 26.5%.[5]

Medications used to treat SAR target biochemical pathways that cause characteristic symptoms. SAR results from the binding of an inhaled aeroallergen to immunoglobulin E (IgE) on the surface of mast cells in the nasal mucosa. An early phase allergic response follows: mast cell degranulation releases preformed inflammatory mediators, such as histamine, tryptase, leukotrienes and prostaglandins, which produce immediate nasal itching and sneezing. Histamine stimulation of the histamine-1 (H1) receptors on sensory nerves causes vascular dilation and increased plasma leakage. Stimulation of parasympathetic (cholinergic) nerve fibers by leukotrienes and other mediators causes mucus secretion from nasal glands. Leukotrienes also increase vascular permeability. The result is nasal discharge and congestion, which is maximal at 15 to 30 minutes. Four to 12 hours after allergen exposure, a late-phase allergic response may occur. The late-phase response consists primarily of nasal congestion and is mediated by the influx and activation of inflammatory T-cells and eosinophils.[2,6,7] Ongoing, prolonged allergen exposure and repeated late-phase responses lead to

progressive inflammation of the nasal mucosa and increased allergen sensitivity. The amount of allergen capable of eliciting an allergic response lessens over time, an effect termed priming. The priming effect is thought to explain the development of mucosal hyper-responsiveness to nonallergen triggers, such as strong odors, cigarette smoke, and cold temperatures.[7,8] It also provides the rationale for initiating effective rhinitis therapies prophylactically before the commencement of pollen season.[9,10]

The diagnosis of AR is based mainly on the history and physical examination.[10] The cardinal symptoms are nasal discharge (rhinorrhea), nasal itching, sneezing, and/or nasal congestion. Many patients also experience symptoms of allergic conjunctivitis, such as itchy and watery eyes.[11] The history of seasonality of symptoms with clear exacerbations, in relation to allergen exposure, help establish a diagnosis of seasonal rhino-conjunctivitis (SARC).

Normally, very low levels of IgE are present in the serum. High serum levels have been detected in as many as 30-60% of patients with AR.[12] Antigen-specific IgE antibodies are the most important *in-vitro* allergy tests in establishing the diagnosis of inhalant allergy.[13] Treatments for AR comprise allergen avoidance and triggering factors, use of appropriate pharmacotherapy, immunotherapy, patient education and follow-up.[14]

CASE HISTORY

In February 2010, a 33-year-old Saudi female mathematics teacher visited her general practitioner and reported suffering from repetitive sneezing, nasal blockage, itching of the nose, watery nasal discharge and a tickling sensation at the back of the throat. These symptoms, she reported, dated back to 8 weeks prior to her visit. She suffered from red, itchy and watery eyes. She also felt dizzy and fatigued. The patient recounted that these symptoms have been reoccurring frequently in early spring and summer since she was in high school, but have been progressively worsening in recent years. Three years earlier, she developed repeated episodes of cough, wheezing and chest tightness. Over the previous three months, she developed two episodes of acute asthma exacerbation and was hospitalized at the emergency department, where she received repeated short-rescue courses of oral steroids.

The symptoms were getting worse, however. The patient complained that her daily activities were disrupted by frequent absences from work and that she was socially embarrassed in the presence of her students and colleagues. Her relationship with her husband, as well as her daily activities, were also disturbed due to these respiratory symptoms. The patient reported that she had no pets at home and that her symptoms were triggered by cold air, tobacco smoke and being outdoors early in the morning. Her husband is a smoker, but she denied history of smoking.

Antihistamine chlorphenamine (Piriton®) tablets, prescribed to her many years ago, were helpful but induced sleep by day. She had used Sodium Cromoglicate (Rynacrom®) 4% nasal spray intermittently and also nasal spray (Otrivine®), with partial response. For chest tightness and wheezing, she used Fluticasone (Flixotide®) inhaler, intermittently, and Salbutamol (Ventolin®) inhaler, when needed. Family history revealed atopic eczema and asthma in her elder child and mother. She resides in Abha city south of Saudi Arabia, a mountainous high altitude city with wide agricultural lands and farms.

On examination, she appeared to be uncomfortable and distressed. Her nasopharynx was congested. Nasal examination showed pale boggy mucous

membranes but no polyps or post nasal discharges were found. The conjunctivae appeared congested and edematous with watery discharge. In addition, the tympanic membranes showed a middle ear effusion. On auscultation, the lungs were wheezy on both sides. Peak expiratory flow rate (PEFR) was 50% of the predicted value.

The result of the Skin Prick Test (SPT) with common inhalant allergens was positive to pollens as follows: Prosopis Juliflora 8 millimeters, Bermuda 4 millimeters, Mugwort 3 millimeters and Timothy 3 millimeters. Total IgE level was high (352.6 IU/ml), and serum specific IgE (sIgE) to Prosopis Juliflora and Bermuda grass was 54.27 IU/ml and 23.44 IU/ml, respectively. Peripheral blood eosinophil count was normal.

Mometasone furoate (Nasonex®) nasal spray was prescribed, 100 micrograms in each nostril once daily. To achieve the maximum benefit, the patient was instructed to avoid the septum when spraying, and to use the medication on a regular basis rather than as needed. Inhaled Fluticasone in a dose of 250 micrograms combined with the long acting bronchodilator Salmetrol 50 micrograms (Seretide®) twice daily was prescribed for 3 months. Cetirizine hydrochloride (Zyretic®) once daily to control nasal symptoms, and Olopatadine (Opatanol®) two drops in both eyes twice daily for control of her ocular symptoms were added to the management plan. She was advised to start treatment two weeks before and to continue therapy through the pollen season. She was advised to discontinue over the counter (OTC) medication and Sodium Cromoglicate spray.

The patient was instructed on the importance of spending as much time as possible indoors with air conditioning during the seasons of spring, summer and fall, and spending as little time as possible outdoors, particularly in the early morning when the pollen count was high.

During follow-up visits, the patient expressed her concerns of using inhaled medications, and fears of developing dependence on them. She expressed her concern over the frequency of her absence from work and the overuse of OTC medications without improvement. These concerns were addressed and the patient was educated about her safety and the importance of compliance to medications.

On her following visit, she did not improve and looked unwell. She expressed concern over the difficulties she encountered in conducting her teaching sessions due to fatigue and lack of concentration. She was compliant on drugs but rhinitis symptoms did not improve. The patient was prescribed an oral Prednisolone course of 25 milligrams daily for 3 days, which was reduced by 5 milligrams per day, and was advised to continue oral antihistamine and inhaled medications.

Because partial clinical improvement was achieved, we opted for specific immunotherapy. Referral to an allergist at the regional hospital was arranged for the patient. After counseling for the pros and cons, the patient was started on sublingual immunotherapy (SLIT) four months before the pollen season, and stopped at the end of the pollen season. The build-up phase was done over six weeks and a maintenance phase protocol was followed with no dose reduction during the pollen season.

The percentage of pollen allergen extract in SLIT solution was as follows: mesquite 40%, Bermuda 20%, Mugwort 20% and Timothy 20%. An allergen extract was prepared in separate vials at different and increasing concentrations of 10, 100 and 300 IR (Index of reactivity).

The patient was followed up for three years. She noticed dramatic improvement of the troublesome allergy symptoms. Work performance, tolerance to daily activities

and sleep significantly improved. Inhaled medications were reduced gradually with antihistamines used intermittently. No oral steroids were required during immunotherapy. She continued SLIT for three years with no recurrence of the symptoms after cessation of treatment.

CASE DISCUSSION

Airway allergic disorders are attributed to aeroallergen exposure. In recent decades, researchers have put forth allergen exposure as a major cause of rhinitis and asthma [15-18], and hence the global increase in exposure to aeroallergens is labeled responsible for the disease[17].

Mesquite (*Prosopis juliflora*) is primarily associated with allergic disease in southwestern United States [19,20], Mexico [21], Saudi Arabia [22], South Africa[23], Kuwait [24], United Arab Emirates (UAE) [25], and India [26]. The legume *Prosopis juliflora* has several varieties [20], and is used for the restoration of desert land and as a wood resource. [22,26] It is found to be a rich and significant source of allergens [23]. In UAE, patients sensitive to prosopis were found to be around forty-five percent[25]. Al-Frayh et al. reported the role of Prosopis pollens as a sensitizing factor in Saudi Arabia [22].

Asthma and allergic rhinitis (AR) co-morbidity refers to the association between asthma and AR. This is due to their physiopathological, epidemiological, and clinical similarities[27-31]. The impact of rhinitis with co-morbid asthma on quality of life is significant. In one study, concomitant asthma with rhinitis caused more physical limitations, higher rate of asthma attacks, more emergency room and GP visits than AR alone did to patients.[7]

In the Allergic Rhinitis and its Impact on Asthma (ARIA) classification, intermittent and persistent rhinitis were proposed to replace seasonal and perennial allergic rhinitis (AR). Our patient was categorized as moderate to severe intermittent AR. The global assessment of the patient's nasal and non-nasal symptom severity score was five. This score was measured with a modified 7-point visual analog scale (score seven indicates unbearably severe symptoms).[32]

Nasal antihistamines are similar in efficacy to oral antihistamines. Combined topical ocular antihistamines, non-steroidal anti-inflammatory drugs, and mast cell stabilizers should be used for associated allergic conjunctivitis, as they significantly reduce ocular symptoms.[33,34]

Intranasal corticosteroid therapy is the most effective medication for treating seasonal allergic rhinitis. Patients should start intranasal corticosteroid two to four weeks before the beginning of the pollen season for the prevention of nasal symptoms of seasonal allergies.[11] Sensory attributes of the nasal spray, e.g. smell and taste, might affect patient compliance.[35] Combination therapy of intranasal corticosteroid and oral antihistamines is beneficial to control severe symptoms; an attempt is made to discontinue one of the agents when symptoms have abated.[36,37] In patients with severe symptoms despite treatment with topical corticosteroids and antihistamines, a better alternative is the occasional, intermittent use of oral prednisolone (0.1-0.2 mg/kg) in the morning of days when the pollen count is high.[37] Leukotriene receptor antagonists are indicated as an adjunct to treatment if the patient showed inadequate response to intranasal corticosteroid and antihistamines.

The mainstay of allergen-specific immunotherapy is inducing tolerance to the causative allergen. The key factor is the anti-inflammatory effect of immunotherapy and is based on switching T cell phenotype which, in allergic subjects, is categorized by a prevalence of the Th2 type and the release of IL-4, IL-5, IL-17, IL-13 and IL-32 cytokines.[38] Immunotherapy results in a Th1-phenotype characterized by increased

IFN-gamma and IL-2 release or by a suppressed Th2 response, through a mechanism of anergy or tolerance. It is now recognized that T-cell tolerance is described by the production of allergen-specific T regulatory (Treg) cells, which generate cytokines, such as IL-10 and TGF-beta with immunosuppressant or immunoregulatory activity. [39,40] The dendritic cells and regulatory T cells promote tolerance by suppressing inflammatory cells and inducing isotype switching of antibodies from IgE to IgG, mainly IgG4, which then block the allergens from binding to IgE located on the surface of mast cells and basophils, thus preventing cell degranulation.[41]

Multiple studies have found the ability of immunotherapy to prevent progression of allergic disease, but more research is needed to confirm the positive preventive role of immunotherapy in allergic diseases.[42]

Immunotherapy based on allergen, in its old-fashioned subcutaneous form, has ample verification of efficacy in allergic asthma, as established by a meta-analysis of 67 double-blind, placebo-controlled studies.[43] However, subcutaneous immunotherapy (SCIT) has a major flaw, specifically seen as a systemic reaction resembling anaphylaxis, that is quite exceptional but may be life-threatening and even lethal.[44] There are other problems of SCIT, which includes the irritation of frequent injections and insecurity concerning the optimal strength of extracts and the stability of allergen mixtures. This encouraged the pursuit for safer ways of administration of allergen extracts. Sublingual immunotherapy (SLIT), which was initiated in the 1990s, ultimately encountered such need while providing a clinical efficacy equivalent to SCIT. [45]

Meta-analyses have made it evident that SLIT is effective in allergic rhinitis by expressively reducing the clinical symptoms; [46-50] however, the efficacy in allergic asthma is still questioned. In fact, in the first meta-analysis, there were inadequate data from patients with asthma, [46] and ensuing analyses gave conflicting results, some even advocating negative conclusions. [48,51]

In conventional SCIT, gradually ascending dosages of the allergen extracts are injected subcutaneously in weekly intervals (up-dose period) until the individual maximum dose is reached (dose-maintenance period). Despite the clear benefits of SCIT in allergic rhinoconjunctivitis and (allergic) bronchial asthma, only a few allergic patients subscribe to this treatment. [52-54] Inconvenience is likely the most common reason for not beginning, or discontinuing, the conventional form of SCIT. [52]

In accelerated SCIT protocols, two to three injections are administered per treatment day with an interval of 30 minutes between the injections in weekly intervals. Accelerated SCIT schedules saves time with the cost of a slightly increased frequency of side effects.[55] However, recent studies have suggested similar safety profile as conventional schedules.[52]

SLIT also requires tolerance of the mouth itching that may occur for a few weeks to months at the onset of treatment. Contraindications for SLIT are mainly the same as for SCIT, including lack of compliance, pregnancy, uncontrolled asthma, immunodeficiency, and autoimmune diseases. For SLIT additionally, oral mucosal diseases can be contraindications if immunotherapy irritates the mucosa.[56]

SCIT can be used by non-modified ("native") extracts with unchanged allergen conformation and chemically modified (polymerized) extracts (so-called allergoids). Allergoids are equivalent in efficacy to that of standard SCIT with low rate of systemic reaction.

The major advantages of allergoids are the low number of injections required to reach

the maximal allergen dose (six injections in the majority of patients) given at 1-week intervals, followed by three additional doses at intervals of 2 weeks. There are few commercially available allergen-specific immunotherapy (SIT) products based on allergoids, whether for subcutaneous injection or as sublingual formulations. Conclusions on the efficacy of allergoid preparations are limited by the amount of published data. Further research is needed to increase the level of evidence for these preparations in SIT.[57-59]

Education is required to increase the patient's knowledge about immunotherapy and compliance. Immunotherapy, in general, is usually not more costly than traditional allergy medications over the projected course of treatment. SLIT, however, has been shown to be more cost effective than SCIT from all perspectives.

CONCLUSIONS

SIT can significantly improve the management, outcome, and quality of life in moderately severe SARC with asthma partially controlled with conventional therapy. Characteristic allergy symptoms with seasonal exposure to pollens and associated clinical features, supported with allergy testing, help establish diagnosis.

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