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Sublingual immunotherapy – a good choice for all forms of birch pollen allergy

Сублингвална имунотерапија – добар избор за све форме алергије на полен брезе

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SUMMARY

Introduction High prevalence of hypersensitivity to birch pollen significantly reduces the quality of life of affected individuals. Control of the simultaneous manifestation of allergic rhinitis and/or asthma and birch–apple allergy syndrome is particularly challenging. Opinions regarding the effects of allergen immunotherapy (AIT) on the control of birch–apple allergy syndrome are divided.

Case outline We present a female patient with poorly controlled allergic rhinitis and asthma due to hypersensitivity to birch pollen and allergy to apples, in whom sublingual immunotherapy (SLIT) with an oral lyophilizate of birch pollen was administered. Nine months of SLIT, added to pharmacological therapy, led to good control of allergic rhinitis and asthma and to the development of apple tolerance.

Conclusion The favorable outcome of SLIT in controlling respiratory allergies and inducing apple tolerance suggests that it may be a beneficial therapeutic option for the management of all clinical manifestations of birch pollen allergy.

Keywords: allergic rhinitis; allergic asthma; pollen–food allergy syndrome; allergen immunotherapy

САЖЕТАК

Увод Висока учесталост преосетљивости на полен брезе, значајно умањује квалитет живота оболелих. Нарочито је отежана контрола истовремене експресије алергијског ринитиса и/или астме и бреза-јабука алергијског синдрома. Мишљења о ефектима алергенске имунотерапије (АИТ) на контролу бреза-јабука алергијског синдрома су подељена.

Приказ болесника Приказујемо пацијенткињу са лоше контролисаним алергијским ринитисом и астмом услед преосетљивости на полен брезе и алергијом на јабуке, подвргнуту сублингвалној имунотерапији (СЛИТ) оралним лиофилизатом полена брезе. Деветомесечна примена СЛИТ, придодата фармаколошкој терапији, довела је до добре контроле алергијског ринитиса и астме и толеранције на јабуку.

Закључак Повољан исход СЛИТ у контроли респираторних алергија и толаранцији на јабуку, указује да би могла бити повољан терапијски избор за контролу свих клиничких облика алергије на полен брезе.

Кључне речи: алергијски ринитис; алергијска астма; полен–храна синдром; алергенска имунотерапија

INTRODUCTION

Birch is the largest producer of allergenic tree pollen in Europe, with a sensitization prevalence ranging between 7% and 57% of the population. Most sensitized individuals have allergic rhinitis and/or asthma, and more than half also develop pollen–food allergy syndrome (PFAS), an immunoglobulin E (IgE)-mediated allergic reaction to foods from fruits and vegetables associated with sensitization to inhalant allergens, most commonly pollen [1,2]. PFAS is based on IgE cross-reactivity to structurally similar, homologous allergens from different protein families present in both foods and pollen. The clinical presentation of PFAS is most often mild (itching and mild swelling of the lips, mouth and throat), and only rarely includes symptoms

of anaphylaxis. PR-10 proteins, profilins and ipid transfer proteins (LTPs) are recognized plant panallergens involved in pollen-food cross-reactivity. Allergens from the pathogenesis-related protein 10 (PR-10) family and profilins are usually responsible for mild clinical manifestations, whereas allergens from other protein families are associated with more severe clinical forms of PFAS. More than 70% of individuals sensitized to birch pollen who have allergic rhinitis and/or asthma develop PFAS due to apple allergy (birch–apple allergy syndrome) [3,4]. The quality of life of affected patients is further reduced, and their management represents a significant therapeutic challenge [5–7]. Avoidance of raw fruit and symptomatic therapy are recommended, while opinions regarding the use of allergen immunotherapy (AIT) remain divided [7,8].

We present a patient with concomitant seasonal allergic rhinitis, asthma and PFAS associated with apple allergy, in whom treatment with sublingual immunotherapy (SLIT) using an oral lyophilizate of birch pollen had a favorable effect on the control of all clinical manifestations of birch pollen allergy.

CASE REPORT

We present a 25-year-old female patient with seasonal allergic rhinitis and asthma due to hypersensitivity to birch pollen and pollen–food allergy syndrome (PFAS), manifested as allergy to apples. The disease began suddenly in the spring of 2009, at the age of nine, with symptoms typical of allergic rhinitis and mild asthma, followed later that year by allergy to fresh apple (pronounced itching, burning sensation in the oral cavity and difficulty swallowing). Based on medical history, clinical examination, spirometry, skin prick testing, and measurement of serum specific IgE (sIgE) to standard inhalant and food allergens, allergic rhinitis and asthma due to hypersensitivity to birch pollen associated with **allergy to apples**

were diagnosed one year later. With regular allergist follow-ups and pharmacological therapy, in accordance with recommendations for moderate-to-severe allergic rhinitis and mild allergic asthma, the patient maintained good control of respiratory symptoms until the end of 2021. In late April 2022 and early April 2023, despite regular therapy, the patient was hospitalized due to a sudden worsening of asthma and severe nasal obstruction. Control of respiratory symptoms was achieved with parenteral methylprednisolone administered in tapering doses. PFAS was successfully controlled by avoidance of fresh fruit. In the family history, the patient's brother, father, and uncle have confirmed diagnoses of allergic asthma. Due to a sudden worsening of breathing during two consecutive tree pollen seasons, the patient presented for examination at the outpatient clinic of the Clinic for Allergy and Immunology, University Clinical Center of Serbia, Belgrade**,** in late May 2023. Investigations conducted in accordance with guidelines for allergic rhinitis, asthma, and PFAS confirmed the diagnoses of moderate-to-severe poorly controlled seasonal allergic rhinitis, mild partially controlled asthma due to hypersensitivity to birch pollen, and PFAS with allergy to apples**.** The diagnosis of allergic rhinitis and asthma was based on medical history and clinical presentation during the March–May pollen season, in correlation with a positive skin prick test exclusively to birch pollen (papule diameter 8 mm; saline solution 0 mm; histamine solution 5 mm) and a high serum concentration of sIgE to birch pollen (30.29 kUA/L, class 4) (ImmunoCAP system, Thermo Fisher Scientific, Uppsala, Sweden). The diagnosis of birch–apple allergy syndrome was established based on the patient's history (itching and burning in the throat and oral cavity and difficulty swallowing immediately after apple consumption), a positive prick-to-prick skin test with apple (9 mm; saline solution 0 mm; histamine solution 6 mm), and elevated serum sIgE to apple (7.80 kUA/L, class 3). Due to poor control of respiratory allergies and long-term avoidance of fresh fruit, component-resolved diagnostics (ImmunoCAP system, Thermo Fisher Scientific, Uppsala, Sweden) was performed with the aim of introducing allergen immunotherapy (AIT). Primary sensitization

to Bet v1, the major allergen of birch pollen, and cross-reactivity to Mal d1, the major apple allergen (PR-10 type), were demonstrated (Table 1). Sensitization to the minor allergens of birch pollen and apple, Bet v2 and Mal d4, was not detected (sIgE Bet v2 0.11 kUA/L, sIgE Mal d4 0.16 kUA/L). Based on these findings, sublingual immunotherapy (SLIT) with an oral lyophilizate of a standardized allergen extract from birch pollen was initiated. A preseasonal and coseasonal protocol was applied for nine months (from early September 2023 to the end of May 2024) in addition to pharmacological therapy. Before initiation of SLIT, a double open oral food challenge with a fresh Granny Smith apple was performed with a cumulative dose of 200 g (one medium apple). The test was positive (visual analog score 8). Symptoms resolved after administration of two tablets of desloratadine. The efficacy of SLIT was assessed based on clinical parameters (Table 2) and laboratory criteria (oral provocation test with fresh apple and serum concentrations of sIgE and sIgG4 to the major allergens of birch pollen Bet v1 and apple Mal d1) (Table 1). During the tree pollen season while receiving SLIT, the patient achieved good control of rhinitis and asthma, and one month after discontinuation she also demonstrated good tolerance to apple, for the first time in more than ten years (Table 1). The favorable outcome of SLIT was accompanied by high serum concentrations of specific IgG4 to the major birch pollen allergen Bet v1 (0.84 mgA/L) and to the cross-reactive major apple allergen Mal d1 (0.62 mgA/L). The patient decided to discontinue SLIT after the first treatment season. During additional follow-up one year after discontinuation of SLIT, the patient maintained well-controlled mild allergic rhinitis and mild asthma (Table 2), but apple tolerance was not maintained. The oral provocation test with a Granny Smith apple was again positive, with a lower score of oropharyngeal symptoms, accompanied by reduced levels of sIgG4 to the major allergens of birch pollen and apple (Table 1).

Informed consent: Written informed consent was obtained from the patient for this case report publication, including the medical history and laboratory analyses.

Ethics approval: The publication of this case report was approved by the Ethics Committee of the University Clinical Center of Serbia.

DISCUSSION

The high prevalence of birch–apple allergy syndrome is part of the global "allergy epidemic" and results from the frequent sensitization to birch pollen and its strong cross-reactivity with apple. In these patients, seasonal allergic rhinitis and/or asthma are often difficult to control with standard pharmacological therapy [9, 10]. This difficulty is attributable to cross-reactivity between birch pollen and homologous tree pollens [11], as well as to the global increase in airborne pollen concentrations [12]. These factors were also the main reasons for the poor control of allergic rhinitis and asthma in our patient. Good control of allergic rhinitis and asthma until 2021 was associated with relatively low concentrations of birch pollen in the environment, which did not exceed 100 pollen grains/m³ of air. However, in the following years very high concentrations were recorded (298–593 pollen grains/m³ of air) during April and May, which coincided with poor control of respiratory allergies. Despite persistently high birch pollen concentrations, SLIT resulted in good control of allergic rhinitis and asthma, not only during treatment but also after its discontinuation. The favorable clinical effect of SLIT was accompanied by an increase in serum concentrations of specific IgG4 and a decrease in specific IgE directed against the major birch pollen allergen, as reported by other authors as well [11, 13, 14]. Nine months of SLIT resulted in good tolerance of fresh apple, accompanied by increased concentrations of sIgG4 and decreased concentrations of sIgE to the major allergens of apple and birch pollen in serum. The significant role of sIgG4 in blocking IgE-dependent cross-reactivity between the major allergens of birch pollen and apple has also been reported by other authors [3, 4, 15]. The blocking role of sIgG4 is directly related to the clinical effects

of SLIT in inducing tolerance to apple in birch–apple allergy syndrome [16, 17]. Identification of the carriers of primary and cross-reactive IgE responses between birch pollen and apple is of great importance for the effectiveness of SLIT in our patient [8, 15, 17]. Although the major birch pollen allergen is the most common carrier of primary sensitization and cross-reactive IgE response to apple, this is not always the case in clinical practice. In approximately 10% of patients, the primary (and only) carrier is the minor allergen Bet v2 or another minor birch pollen allergen [17, 18]. In such patients, SLIT unfortunately does not lead to tolerance to apple. A considerable number of studies, in which SLIT efficacy was not demonstrated, lack evidence on the carriers of cross-reactive IgE responses with apple [19]. The favorable outcome of SLIT in our patient was also influenced by the daily administration of an oral lyophilizate containing a high concentration of the major birch pollen allergen and by the absence of sIgE to minor allergens of birch pollen and apple. The beneficial effect of SLIT in establishing tolerance to apple was not sustained to the same extent as the control of respiratory allergies. Six months after discontinuation of SLIT, the patient reported oral itching associated with apple consumption for the first time. During further follow-up, itching occurred occasionally, after consumption of only certain apple varieties, and resolved spontaneously. One year after discontinuation of SLIT, the repeated oral provocation test with apple was again positive. Although the score was low, it negatively affected the patient's choice of fruit. The gradual loss of tolerance to apple was accompanied by a heterogeneous decrease in serum concentrations of sIgG4 to the major allergens of birch pollen and apple, as also reported by other authors [17, 19]. Several explanations for the failure of SLIT in controlling birch–apple allergy syndrome have been described in the literature. The most common reason is insufficient knowledge of the allergens responsible for cross-reactive IgE responses between birch pollen and apple [3, 8], structural variations of the major apple allergen among different apple varieties [17], and insufficient maintenance dose or short duration of treatment [8, 9]. Recent studies

indicate that SLIT-induced sIgG4 directed against the major birch pollen allergen blocks all IgE-binding epitopes on Bet v1 but not on Mal d1. A high degree of cross-reactivity of sIgG4 directed against Bet v1 toward Mal d1 requires a high degree of structural homology between the major allergens of birch pollen and apple (above 80%), which in reality does not exceed 56% [16, 20]. This is assumed to be the main reason for the limited efficacy of SLIT in controlling birch–apple allergy syndrome. It has been established that sIgG4 directed against the major apple allergen binds different epitopes from those recognized by sIgG4 directed against the major birch pollen allergen. For effective blocking of IgE-binding epitopes on the major apple allergen—and consequently for successful SLIT-induced tolerance to apple—a high concentration and high affinity of sIgG4 directed toward different epitopes of the major apple allergen are required. An increase in their serum concentration is usually detected after four months, while maximal concentrations are achieved only after long-term SLIT administration lasting at least three years [21]. The efficacy of SLIT in our patient is consistent with these findings [21, 22, 23]. Tolerance to apple was gradually lost due to premature discontinuation of SLIT, which represents the main limitation of this case report. Nevertheless, the favorable outcome observed in our patient suggests that, under certain conditions, SLIT may represent a good therapeutic option for the control of all clinical manifestations of birch pollen allergy.

Conflict of interest: None declared.

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Table 1. Results of allergological tests and laboratory findings

Features	Before SLIT	One month after SLIT	12 months after SLIT
Skin prick test to birch pollen (wheal diameter in mm)	8	7	8
Skin prick to prick test to apple (wheal diameter in mm)	9	9	8
Oral apple provocation test (visual analogue score)	8	0	3
sIgE Bet v1 (kUA/L)	31.08	26.90	25.89
sIgE Mal d1 (kUA/L)	8.09	7.53	7.11
sIgG4 Bet v1 (mgA/L)	0.09	0.84	0.75
sIgG4 Mal d1 (mgA/L)	0.06	0.62	0.31

SLIT – sublingual immunotherapy; sIgE – specific immunoglobulin E; sIgG4 – specific immunoglobulin G4; Bet v1 – Betula verrucosa 1 major allergen; Mal d1 – Malus domestica 1 major allergen

Table 2. Control of allergic rhinitis and asthma before, during and after SLIT

Features	Season 2022 before SLIT	Season 2023 before SLIT	Season 2024 during SLIT	Season 2025 after SLIT
AR VAS	8.66	8.33	2.66	2.73
ATDMS AR	5.16	6.49	1.38	1.32
ATDMS A	2.08	2.55	0.66	0.52
Number of severe AE	1	1	0	0
ACT	16	15	21	22

AR – allergic rhinitis; A – asthma; VAS – visual analogue scale; AE – asthma exacerbation; ATDMS – average total daily medication score; ACT – asthma control test; SLIT – sublingual immunotherapy

