

Malignancy and Specific Allergen Immunotherapy: The Results of a Case Series

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Key Words

Allergy · Allergen vaccination · Cancer · Contraindication ·
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Abstract

Background: Specific immunotherapy with allergen is the only causative treatment for IgE-mediated allergies such as stinging insect allergy or hay fever and works by the induction of blocking antibodies and regulatory T lymphocytes. **Objective:** Does a hypothetical obstruction of tumor surveillance presupposing the induction of regulatory T cells really justify detaining immunotherapy to oncologic patients as suggested by recent guidelines? **Methods:** We report 6 patients (4 female, 2 male) suffering or having suffered from stage 1 cancer (4 melanomas, 1 lung cancer, 1 breast cancer) and concomitant IgE-mediated allergy. Four of them had a history of severe anaphylactic reactions to the insect yellow jacket, the 5th suffered from allergic rhinoconjunctivitis to dust mites, and the 6th to grass/rye pollen. **Results:** Between 2004 and 2010, subcutaneous immunotherapy was safely performed in 5 patients without signs of tumor reactivation. The cancer in 2 of them was diagnosed immediately after specific immunotherapy had been initiated and in another 2 the active cancer phase had already finished years before;

the 5th suffered from a relapse around the time of the initiation of immunotherapy. At the time of the writing of the manuscript, 4 of them had already concluded 3 years of treatment, another one almost 1 year. The melanoma in the 6th patient was diagnosed 5 months after reaching the maintenance dose. Immunotherapy with grass/rye pollen was aborted in this patient based on current guidelines.

Conclusions: Specific immunotherapy was safely administered in patients suffering concomitantly from IgE-mediated allergy and lower stage cancer.

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Introduction

Specific immunotherapy (SIT) with allergen is the only causative treatment for IgE-mediated (type I allergic) diseases. Its efficacy is well established in the context of allergic, anaphylactic reactions to hymenoptera venom as well as in the treatment of allergic rhinoconjunctivitis (ARC) and allergic bronchial asthma. The exact pathomechanism is still a matter of debate but three hypotheses are currently regarded as the most probable ones: first the shift of Th₂ to Th₁ cytokines, second the induction of so-called allergen-specific ‘blocking’ IgG₄ (and maybe also IgG₁) antibodies, and third the induction of T cell toler-

Table 1. Overview of the patients

Patient	Sex	Age at initiation of SCIT	Grade of anaphylaxis [2]	Initial clinical symptoms of allergy	Allergen	Date of initiation of SCIT
1	F	77	IV	fall in blood pressure, dyspnea, cynosis, collapse	YJ	February 2004
2	M	33	IV	collapse and unconsciousness (repeatedly)	YJ	July 2004
3	F	46	IV	collapse and unconsciousness	YJ	September 2006
4	F	63	III	dyspnea and large local reaction	YJ	March 2010
5	F	39	n.a.	perennial, moderate to severe ARC [1]	dust mite	April 2007
6	M	38	n.a.	seasonal, ARC	grass/rye	September 2008

Severity of anaphylaxis is graded according to Mueller [8]. n.a. = Not available.

ance mainly via peripheral, IL-10- and TGF- β - secreting Fox-p3-positive regulatory T cells [1–3]. Although SIT is highly efficacious and allergen specific, the induction of T cell tolerance raises hypothetical concerns that SIT may not be appropriate in patients suffering or having suffered from cancer because some unspecific bystander tolerance induction might compromise the host's immunological tumor surveillance [1]. Breaking the tolerance to tumor cells by specific targeting of regulatory T cells has been successfully used in experimental cancer treatment such as advanced melanoma [4].

Although there is no published evidence for an increased risk of cancer induced by SIT or cancer relapse in patients under SIT, these theoretical concerns led to the inclusion of cancer or a recent history of cancer as contraindication for the initiation of SIT into the recent German-Swiss-Austrian guideline for SIT [5]. We want to point out that patients actually suffering from active cancer or having suffered from cancer earlier in their life can still suffer from IgE-mediated allergies and their symptoms cannot always be sufficiently treated by symptomatic, pharmacological medication. Hence, SIT is sometimes required as an additional therapeutic option in these patients suffering from active or latent cancer.

Herein, we report a case series of 5 patients in whom SIT was safely initiated, and in 4 of them continued for at least 3 years and in another one for three quarters of a year. The cancer in 2 of these patients was diagnosed at the same time as SIT was initiated and in 3 of the others the active phase of cancer had already finished years before. We additionally report another patient in whom an ongoing SIT was stopped after half a year because of the diagnosis of a thick, acral melanoma. This decision was based on the recent German-Swiss-Austrian guideline for SIT [5].

Patients and Methods

All 4 patients with a history of vespid-sting reactions (No. 1–4) were submitted to skin prick tests (SPT; table 1). Upon negative SPT, titrated intradermal tests (IDT) were performed with 0.05 ml subcutaneously injected aqueous yellow jacket (YJ) solution at concentrations of 0.01, 0.1 and 1 μ g/ml (all solutions from ALK-Abelló, Linz, Austria) in the volar forearms. SPTs from a diameter of ≥ 3 mm and IDTs from a diameter of ≥ 5 mm were considered positive in accordance with the German guideline on the interpretation of allergy skin tests [6] (table 2). Specific IgE, total IgE and tryptase (all on ImmunoCAP®; Phadia, Uppsala, Sweden) were determined in all patients. Rush subcutaneous immunotherapy (SCIT) was performed as a 5-day inpatient regimen as reported previously [7] with aqueous Alutard SQ® (ALK-Abelló). The conventional build up and the maintenance injections for all were done with the standard, aluminium-hydroxide-coupled Alutard SQ (ALK-Abelló) according to the manufacturer's standard protocol. The maintenance dose for both regimens was 100,000 SQ units and delivered every 4 weeks. The severity of the anaphylactic reactions was graded according to the criteria by Mueller [8].

Patient 5 suffered from perennial ARC (table 1). The house dust mite allergy was treated with a house dust mite allergoid (Ac-aroid®; Allergopharma, Reinbek, Germany) according to the manufacturer's standard regimen with maintenance injections every 4 weeks.

Patient 6 suffered from seasonal ARC in late spring to early summer (table 1). SCIT was initiated with a standard grass/rye pollen preparation (Alutard SQ; ALK-Abelló) according to the manufacturer's standard regimen with maintenance injections every 4 weeks.

Patients 1–5 gave informed consent for SCIT with a special emphasis on the relative contraindication for cancer, patient 6 gave standard consent for the initiation of SCIT.

Case Series

Patient 1

In 2004, a woman of 77 years developed a grade IV reaction consisting of severe dyspnea and collapse after a YJ sting (table 1). Allergy to YJ venom was confirmed by a positive IDT at 0.1 μ g/

End of SCIT	Type of SCIT up dosing	Type of tumor	Diagnosis of tumor	Months between initiation of SCIT and tumor diagnosis
October 2009	conventional	breast cancer	November 1993	>120
October 2009	rush	melanoma	May 2004	0
September 2011 (planned)	rush	melanoma	September 2006	0
ongoing	rush	lung cancer	June 1994	>120
March 2010	conventional	melanoma	June 1993	168
May 2009 (aborted)	conventional	melanoma	March 2009	-6

Table 2. Allergological details

Pa-tient	Allergen	Wheal diameter of SPT, mm ^a	Diameter of IDT mm ^a	Positive in titrated IDT at	Serum tryptase, µg/l (normal ≤11.4)	Allergen-specific IgE before SCIT kU/l (normal <0.35)	Total IgE kU/l (normal ≤100)	Comments
1	YJ	negative	6.5 mm	0.1 µg/ml	10.3	1.28	37.4	
2	YJ	negative	8 mm	0.1 µg/ml	41	<0.35	9.33	additional diagnosis: cutaneous and indolent systemic mastocytosis
3	YJ	negative	7.5 mm	0.1 µg/ml	4.8	30.8	434.0	
4	YJ	5 mm (300 µg)	n.d.	n.d.	5.7	0.75	31.8	additional diagnosis: ARC
5	dust mite	6 mm	n.d.	n.d.	n.d.	15.1	174.0	significant clinical improvement after SCIT; additional diagnosis: aspirin intolerance
6	grass/rye	4.5 mm	n.d.	n.d.	n.d.	7.0	222.0	additional sensitization: dust and storage mite

n.d. = Not determined.

^a Allergological details: the diameter was determined by applying the following formula: diameter = (longest diameter + shortest diameter)/2.

ml and specific IgE to YJ venom (table 2). She additionally suffered from heart disease with hypertension and intermittent atrial fibrillation.

Breast cancer had been diagnosed in 1993 (table 3). She had been subjected to surgical ablation of the right breast and tamoxifen (Nolvadex®; Corden Pharma, Plankstadt, Germany) as additional adjuvant hormonal therapy. The cancer had been classified as stage 1 disease [9]. In the further course, the patient was surveyed for a decade with no signs of recurrence until 2003, when follow-up was closed.

We initiated conventional SCIT with hymenoptera venom (VIT) with YJ venom in spring 2004. However, 3 months after having reached the maintenance dose the patient experienced a local tumor relapse in 3 draining axillary lymph nodes on the right side. The patient was submitted to total lymphadenectomy of the right axilla, partial excision of the Latissimus dorsi muscle plus local radiation therapy. The tumor was restaged to 3b (table 3). In the further course, the tumor could be stabilized under adjuvant chemotherapy with trastuzumab (Herceptin®; Roche,

Grenzach-Wyhlen, Germany) and the estrogen receptor antagonist fulvestrant (Faslodex®; AstraZeneca, UK). The VIT in monthly intervals was completed in autumn 2009.

Patient 2

A 33-year-old man collapsed and fell unconscious twice after two independent YJ stings. Allergological work-up of these grade IV reactions [8] revealed a positive titrated IDT to YJ venom at 0.1 µg/ml (table 2). YJ venom-specific IgE remained (possibly false) negative, at a same time very low total IgE of <10 kU/ml was detected. Hence, we based the diagnosis YJ allergy on the positive IDT and the history of the 2 well-documented reactions to YJ stings.

On dermatological inspection, the patient was densely covered with a multitude of brownish-orange patches with a positive Darier sign. A punch biopsy confirmed cutaneous mastocytosis. Together with the results of the bone marrow biopsy showing 5% atypical mastocytes bearing the D816V mutation in the c-kit gene we made the final diagnosis YJ allergy aggravated by systemic

Table 3. Oncological details

Pa-tient	Histopathology and location	Tumor relapse	TNM	Clinical staging	Tumor follow-up
1	lobular breast cancer; right	yes (2004)	T2 N0 M0	1 at initiation of SCIT, 3b after relapse [9]	1993–ongoing
2	superficial spreading melanoma, Clark level III, Breslow index 0.45 mm; back	no	T1a N0 M0	1a [12]	2004–ongoing
3	superficial spreading melanoma, Clark level III, Breslow index 0.5 mm; upper arm	no	T1a N0 M0	1a [12]	2006–ongoing
4	peripheral adenocarcinoma; lower right lobe	no	T1 N0 M0	1a [11]	1994–2004
5	superficial spreading melanoma, Clark level III, Breslow index 0.6 mm; upper right back	no	T1a N0 M0	1a [12]	1993–2002
6	acral lentiginous melanoma, Clark undetermined, Breslow index >1 mm; subungual left thumb	no	T2b N0 M0	1b [12]	2009–ongoing

The clinical staging is according to current guidelines on the staging of melanoma [12], breast cancer [9] and lung cancer [11].

mastocytosis [10]. VIT with YJ venom following our standard 5-day in-patient rush protocol followed by monthly maintenance doses was initiated [7].

During the time on the ward, when the patient had already reached the maintenance dose, a suspicious, brown macula was removed from the patient's back. The histopathology showed superficial spreading melanoma with a Breslow index of 0.45 mm (table 3). Staging for the melanoma as well as the systemic mastocytosis revealed no signs of metastases. After surgical revision of the melanoma with a safety margin of 1 cm the patient remained tumor free and in remission for the next 6 years. The YJ-VIT could be completed after 5 years in autumn 2009.

Patient 3

A 46-year-old woman collapsed and lost consciousness after a YJ sting into the left shoulder (table 1). The allergological work-up of this grade IV reaction revealed a positive IDT at 0.1 µg/ml and high specific IgE to YJ venom (table 2). The patient was submitted to rush VIT with monthly maintenance treatment.

Much the same as patient 2, a suspect brown macula was removed from the upper arm during the time on the ward. Histopathology proved superficial spreading melanoma, Breslow index 0.5 mm (table 3). After surgical revision with a safety margin of 1 cm and staging that revealed no signs of systemic disease, the patient remained tumor free and in remission for >4 years.

The YJ-VIT was continued at monthly maintenance intervals and the completion of 5 years is scheduled for summer 2011.

Patient 4

In late summer 2009, within minutes after a YJ sting a 63-year-old woman experienced severe dyspnea and a large local reaction. The allergological work-up of this grade III reaction showed a positive reaction in the titrated SPT to 300 µg and a low specific IgE to YJ venom (table 2). We initiated conventional SIT with YJ venom in March 2010. The patient received monthly maintenance therapy and the SIT will be continued until 2015.

In contrast to patients 1–3 and 6, this patient did not suffer from an active or recent but from a latent, peripheral adenocarci-

noma of the lung 15 years before. The cancer had been treated by lobectomy of the lower right lung lobe and sentinel lymphadenectomy. The adjacent lymph nodes were tumor free, so the clinical tumor stage had been 1a [11]. The patient remained tumor free for the next decade when the tumor-specific follow-up had been closed 5 years before the initiation of VIT.

Patient 5

This is the case of a 39-year-old female presenting with perennial ARC. She had been diagnosed as house dust mite-allergic years before (table 1). Thorough dust mite avoidance measures including mattress encasings and additional symptomatic therapy with systemic topical nasal corticosteroids, histamine eye drops and systemic antihistamines had remained without success.

Back in 1993, the patient had suffered from a superficial spreading melanoma with a Breslow index of 0.6 mm. After surgical removal with a safety margin of 2 cm the patient had remained relapse free for the next decade.

In contrast to patients 1–4, ARC is not a life-threatening condition. However, patient 5 was very determined about her wish to receive SIT and, hence, 14 years after her melanoma, conventional SCIT with a house dust mite allergoid was initiated in 2007. The SCIT was completed 3 years later in the summer of 2010 when the patient reported significant improvement of her allergic symptoms.

Patient 6

The case of patient 6 is different. This 38-year-old male patient suffered from seasonal ARC in late spring to early summer. Grass/rye pollen allergy was confirmed by SPT and in vitro test (table 2) and conventional SCIT with a commercial grass/rye pollen extract was initiated after the end of the pollen season in autumn 2008.

In April 2009, a subungual acral lentiginous melanoma on the left thumb with a Breslow index >1 mm was diagnosed (stage 1b; table 3) [12]. The distal phalanx of the left thumb was amputated. The staging including sentinel lymph node analysis showed neither local nor distant metastasis.

Because ARC is not a life-threatening condition, the SCIT was terminated in accordance with current guidelines [13]. Quarterly check-ups for the next 1.75 years until the writing of the manuscript revealed no signs of melanoma relapse.

Discussion

In this case series, we present 4 different constellations of cancer and SIT and describe the way we handled these situations:

- (I) life-threatening hymenoptera allergy and latent cancer (patients 1 and 4);
- (II) life-threatening hymenoptera allergy and active cancer (patients 2 and 3);
- (III) bothersome allergy and latent cancer (patient 5);
- (IV) bothersome allergy and active cancer (patient 6).

A physician's decision to sideline facultative contraindications such as latent cancer when a patient presents with a potential life-threatening hymenoptera venom allergy is a relatively easy task. Hence, the clinical experience with patient 1 under VIT from 2004–2009 prompted us to opt for the same treatment strategy for patient 4 in 2010.

Patient 1 experienced a relapse of her breast cancer only 3 months after having reached the maintenance dose. The question arose whether there was a connection between the initiation of VIT and the tumor relapse only 3 months later. Usually, tumors do not grow so fast as to reach a size of 6 cm within a time span of only 3 months. Hence, in our eyes the relapse must have already occurred long before the initiation of the VIT. The tumor could be stabilized in stage 3. Assuming that there was no connection between tumor relapse and immunotherapy, we continued the VIT in monthly intervals until 2009 when we finally completed the recommended 5-year therapy. In late 2010, over a year after the end of the VIT, the patient's tumor is still well controlled.

The melanomas of patients 2 and 3 were diagnosed in 2004 and 2006, while the patients were on the ward for the rush VIT. The suspect lesions were biopsied on the day of admission and the histological diagnosis was not known before the maintenance dose had been reached. Hence, these special constellations did not require any decision because the patients already were under maintenance therapy before the melanomas were known. The only decision to be made was not to stop the VIT. We kept the patients on maintenance therapy because we rated a potential damage to the patients' health by another YJ sting without VIT higher than a hypothetical induction

of a tumor relapse. Patient 3 already completed the 5 years of VIT, 4 has already safely done 4 years of VIT.

Cases 5 and 6 were different. Both patients suffered from ARC, a bothersome but definitely not life-threatening condition. Patient 5 had suffered from lung cancer more than a decade ago and was very demanding in receiving dust mite SIT for her perennial ARC. The SCIT was safely delivered for 3 years until 2010 without any cancer reactivation and a good clinical result.

The situation of patient 6 was different and a major impetus for the writing of the manuscript. This patient was a 'normal' allergy patient suffering from seasonal ARC. He was put onto SCIT in autumn 2008. By chance, a rare subungual melanoma was diagnosed in April 2009. At that time, we started a thorough literature search and found no evidence supporting the continuation of the SIT and overruling the contraindication cancer mentioned in the at that time brand-new German-Swiss-Austrian SIT guideline [5]. The SIT was stopped after only 5 months of maintenance therapy and the patient was put back onto symptomatic treatment. However, the authors still doubt whether this really was a necessary and inevitable requisite.

Contraindications in SIT have always been a matter of debate. There are mainly two types of contraindications for SIT.

(I) Contraindications because rare anaphylactic side effects of a SIT might acutely aggravate an underlying disease such as severe asthma or heart disease; also a co-medication might diminish the treatment of anaphylaxis with epinephrine such as β -blockers or ACE inhibitors.

(II) Contraindications in which the immune-modulating effects of the SIT might be disadvantageous for underlying, chronic conditions, such as autoimmune diseases, HIV infection, advanced age and last but not least cancer.

As SIT has been used safely for decades, the safety of this treatment modality has become more and more evident and, hence, recent guidelines have dropped some of the more hypothetical contraindications, such as advanced age [5]. Nevertheless, the management of patients with malignancies and concomitant type 1 allergy remains an area of uncertainty with hardly any publications in the medical literature. Some of the more recent guidelines such as the new German-Swiss-Austrian guideline on SIT lists malignancies as contraindication [5], other recent guidelines, for example the 2007 joint American one [14], the European ARIA guideline from 2008 [15] and the World Allergy Organization position paper of 2009 [16], do not touch on this matter at all.

In the context of the lack of data concerning SIT and concomitant neoplasia, there is a big exception for a very special, benign tumor with lots of published data: mastocytosis. Only a little more than a decade ago, it was standard to treat mastocytosis patients suffering from hymenoptera venom allergy with emergency kits only [17]. Nowadays, the treatment strategy has been completely reversed and these patients, for example case 2, are seen as those who require VIT the most [18], sometimes even at increased maintenance dose [19]. Clinical experience had to be gathered before VIT could become an accepted treatment of choice for hymenoptera venom-allergic mastocytosis patients [10]: (I) the clinical experience that the immediate anaphylactic side effects of patients with high numbers of mast cells are usually infrequent, mild and can be well managed; (II) the clinical experience that SIT does not influence the tumor itself.

The reason why evolution has ‘invented’ IgE that (in our modern eyes) does more harm than good has been a matter of debate for a long time. Lately, the idea that IgE might have some role in tumor surveillance was brought up and even a new term was introduced: ‘allergo-oncology’ [20]. This debate was mainly spurred by two observational studies from Australia [21] and the USA [22] describing a scarce, yet significant inverse association of allergy or asthma and the occurrence of cancer. Even the published discussion immediately after the publication of the second study brought up the notion that several confounders such as the use of allergy and asthma medication might pose important confounding factors [23]. Other epidemiological studies have shown differing results for different types of cancer, for example a protective

effect (negative association) between atopy and colorectal cancer or leukemia and a positive association between atopy and lung or prostate cancer [21, 24, 25]. Thus, a new research field was opened and the discussion is still ongoing.

Conclusion

Summing up, based on our limited experience we believe that the hypothetical risk of influencing an underlying oncologic disease by SIT seems to be rather low. To finally resolve this important issue, studies with large patient cohorts and long postintervention follow-up periods are urgently required.

However, we think that at least low stage cancer may not pose a necessary contraindication for SIT. This could make SIT available for an aging population with an increased incidence of cancer who, however, is still suffering from IgE-mediated allergies [26]. We suggest that cancer could be removed from the guidelines as contraindication to SIT because otherwise many physicians will remain reluctant in prescribing this as an option to the rare patients concomitantly suffering from cancer and type 1 allergy.

Disclosure Statement

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