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THE INFLUENCE OF MEDICAL ECONOMY FROM THE ASPECT OF MEDICAL DIRECT COSTS BY A DIFFERENCE OF THE NUMBER OF THE POLLEN SCATTERING ON AN ALLERGEN-SPECIFIC IMMUNOTHERAPY FOR JAPANESE CEDAR POLLINOSIS

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**Background:** We studied medical economic efficacy and influence by the different number of pollen scattering in patients treated with allergen-specific immunotherapy for Japanese cedar pollinosis.

**Methods:** We calculated medical treatment costs and the medicine expense from medical records in eighteen cedar pollinosis patients treated with allergen-specific immunotherapy (IT-G) and with medications (M-G). We examined with the same patients for three years of different pollen scattering, mass scattering year (2005), moderate scattering year (2003), a few scattering year (2004). Furthermore, satisfaction of treatment and symptom score measured by visual analog scale in both subjects was studied in a mass scattering year.

**Results:** Total medical costs at hospital was cheaper in IT-G than in M-G. The result was depended on prescribed medical costs. In addition, prescribed medicine agents and total medical costs did not increase by the mass scattering year of pollen. Satisfaction of treatment and symptom score in IT-G was better than that in M-G.

**Conclusion:** Immunotherapy had a benefit on a medical economy.

## 厚生労働科学研究費補助金(免疫アレルギー疾患予防・治療研究事業)

### 研究報告書

#### リアルタイムモニター飛散数と現状の治療による QOL の関連性の評価研究と花粉症根治療法の開発 スギ抗原特異的メモリーT(IL-4,IL-5,IL-10)細胞の季節変動に関する研究

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#### 研究要旨

スギ花粉症の患者に第2世代抗ヒスタミン薬あるいは鼻噴霧用ステロイド薬にて初期療法を施行し、鼻噴霧用ステロイド薬による初期療法が本格飛散初期の症状を有意に軽減する効果が確認された。花粉症治療に対する患者満足度を向上させるためには、抗炎症作用に優れた薬剤を早期から使用し、飛散ピーク時にはすみやかに併用療法に移行する治療法の確立が必須であり、今後更なるデータの蓄積を必要とする。

#### A 研究目的

スギ花粉症はいまや国民病とも言えるほどに患者数が急増している。スギ花粉症は自然緩解の可能性が少なく、ひとたび発症すると長年にわたり症状に悩まされ、QOL 改善あるいは医療経済的にも根本的治療法が求められるところである。ところで、スギ花粉症を含めたアレルギー性鼻炎に対する特異的免疫療法は、現在のところ唯一根治が望める花粉症の治療法として WHO のポジションペーパーにも記載され、なかでも近年副作用の少ない舌下免疫療法に至っては、欧米では主流となりつつあり日本においてもその普及に関して大いに期待されている。

さて、抗原特異的免疫療法の作用機序については、抗原刺激による Th2 サイトカイン (IL-4, IL-5) の産生抑制に加え、最近では調節性 T 細胞 (Treg) への作用が注目され、特異的免疫療法による調節性 T 細胞 (IL-10 産生) の増加について多くの報告がなされている。我々は、末梢血を用いて抗原特異的メモリー T 細胞を検出する新しい方法を確立し、ダニ抗原特異的メモリー T 細胞の特異的免疫療法による変動について報告してきた。それによると、IL-10 産生抗原特異的メモリー T 細胞は免疫療法により増えることが示唆されている。今回はその予備調査として、スギ花粉症における花粉飛散前、飛散ピーク時、飛散終了後におけるスギ抗原特異的メモリー T 細胞の変動について、主に正常群とスギ花粉症の薬物療法群において検討を行ったので報告する。

#### B 方法

対象は、2006 年のスギ花粉症シーズンにスギ花粉症

にて薬物療法を受けた患者 (患者群) とスギ花粉症およびダニなどの吸入抗原に感作されていない健常者 (コントロール群) である。それぞれの患者および健常人から、2006 年の花粉飛散前、花粉飛散ピーク時期、花粉飛散終了後に採血を行った。採取した末梢血を用い比重遠沈法にて単核球層を分離した。6 穴プレートにて分離した細胞を 3 時間培養した。付着細胞と浮遊細胞を分離し、付着細胞より樹状細胞を誘導した。浮遊細胞は -80°C に保存した。付着細胞を 6 穴プレートにて GM-CSF, IL-4 存在下で 1 週間培養後、標準化スギ抗原 (Cry j 1, 2) と浮遊細胞を入れて overnight で培養した。IL-4, IL-5, IL-10 ELISPOT ASSAY KIT を用いてスポットを染色し、それぞれのサイトカイン産生細胞数として電算画像処理にてカウントを行い、スギ抗原特異的メモリー T 細胞の変化についてそれぞれの群で検討を行った。なお、本研究は山梨大学の倫理審査委員会の承認を受けている。

#### C 結果

まず、コントロール群においては、花粉飛散前、花粉飛散ピーク時及び花粉飛散終了後いずれにおいても、Th2 サイトカイン (IL-4, IL-5) 産生スギ抗原特異的メモリー T 細胞は低値で花粉飛散による変動は認めなかった。しかしながら、スギ抗原特異的 IL-10 産生メモリー T 細胞は、シーズン終了後においてシーズン前に比較し有意に高値を示した。一方、患者群においては、Th2 サイトカイン (IL-4, IL-5) 産生スギ抗原特異的メモリー T 細胞は花粉飛散前の値に比較して徐々に増加する傾向がみられた。しか

しながら、IL-10 産生メモリーT 細胞数は飛散前から高値を示し、季節変動は認めなかった。シーズンを通し、Th2 サイトカイン産生メモリーT 細胞は患者群でコントロール群に比較して有意に高値であった。IL-10 産生メモリーT 細胞数は、飛散前からピーク時までは患者群で有意に高値であったが、飛散終了後は両群間で有意差を認めなかった。

#### D 考察

今回の検討では、スギ抗原特異的メモリーT 細胞 (Th2 サイトカイン (IL-4, IL-5) および IL-10) は、患者群においてコントロール群に比較して有意に高いことが確認された。また、正常群では、スギ花粉吸入により、抗原特異的メモリーTreg 細胞が誘導されている可能性が示唆された。一方、患者群では、すでに抗原特異的メモリーTreg 細胞は誘導されているが、これらが機能的に Th2 細胞を抑制できるものであるかどうかについては不明である。アレルギー患者では Treg の機能障害を示唆する論文もあり今後検討を要する。パイロットスタディとして行ったスギ抗原による免疫療法群による IL-10 産生メモリーT 細胞の検討においては、免疫療法群と薬物療法群の間でその数に有意な差は認めなかった。IL-10 産生細胞の免疫療法による誘導に関してはその早期に起こるとしている文献もあり、免疫療法早期における IL-10 の役割については現在解析を進めている。さらに花粉症においては、毎年花粉飛散数の変動が認められるために、シーズン中におけるこれらメモリーT 細胞の変動について言及する場合には慎重を要すると考えられた。

#### E 結論

スギ花粉症患者においては、抗原特異的 Th2 ならびに IL-10 産生メモリーT 細胞の有意な増加が認められる。今後免疫療法によるこれらメモリーT 細胞の変動ならびに IL-10 産生 T 細胞の機能解析について検討を要すると考えられた。

#### F 健康危険情報

なし

#### G 研究発表

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#### H 知的財産権の出願・登録状況

1. 特許取得  
なし
2. 実用新案登録  
なし
3. その他  
なし

# Nasal Immunologic Reactivity, Rhinitis, and Polyps

## Chapter 87

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## NASAL IMMUNITY: IN DEFENSE OF THE NOSE

### Physiologic surveillance of the nose against inhaled foreign bodies

The nose provides the first line of defense from inhaled foreign and potentially harmful agents. The nose performs these defensive functions by a variety of constituent parts, which are all in attunement toward nasal harmony commencing with the first line of defense: the olfactory system and mucociliary protection of the nasal cavity against foreign bodies. A second line of defense involves the cellular responses by epithelial cells (Hulsman and De Jongste, 1996), macrophages, dendritic cells (DCs), and natural killer (NK) cells. A final line of defense includes immune responses to the target antigens. These combined defensive features function to provide humans with a finely tuned nasal immune defense mechanism, which is in effect mucosal immunity.

Anatomic structures of the nose include the conchas (*i.e.*, superior, middle, and inferior); the nasal septum, which bifurcates vertically into right and left ventricles; four paranasal sinuses (maxillary, ethmoid, frontal, and sphenoid); and the laryngeal structure. These structures develop from bone and cartilage and are covered by mucous membranes. The mucous membrane epithelium consists of ciliated columnar epithelium, goblet, olfactory epithelial, and squamous cells. The resistance of the upper respiratory tract requires ~50% of the total airway. In this region, an extensive array of blood vessels occurs throughout the mucous membrane. The blood

vessels act as a thermoregulator, adjusting the temperature and humidity of the inspired air. Regulation of inspired air to the body's ever-changing dynamics is somewhat analogous to an air conditioner. As air enters the upper respiratory tract through the nose, it is warmed by its blood supply. Nasal secretions from glandular and goblet cells form a mucous blanket, thus softening the irritation from the foreign substances present. Subsequently, the enveloped substances are transported by ciliar motion. This mucociliary function is similar to filtration. Furthermore, as an irritant in foreign substance stimulation, the trigeminal nerve, which widely innervates in the subepithelial and intercellular spaces of the epithelium, transmits the stimulatory response to the central nervous system (CNS), resulting in a "sneeze reflex." The efferent parasympatricotony is mediated by the CNS (Lund, 1996). These physiologic functions are mainly controlled by the autonomic nervous system, which is widely distributed in the nasal mucosa. The previously described defensive mechanisms against inhaled foreign substances are a direct consequence of physiologic expression (*i.e.*, sneezing, rhinorrhea, nasal obstruction, and malodorous avoidance behavior).

## IMMUNOLOGIC SURVEILLANCE OF THE NOSE AGAINST INHALED IMMUNOGENS

### Induction of a nasal immune response

Induction of the nasal immune response at the mucous membrane interface in normal respiration follows these

processes. First, the inhaled air travels through the nostril passageway, then through the middle nasal meatus. This inhaled air, in turn, reaches the nasopharyngeal region. Microorganisms can invade and infect the mucous membrane by means of their motility. The inorganic segment of the inhaled substances is trapped by the mucous blanket, where it becomes dissolved in the mucus secretion and absorbed into the nasal mucosa. The foreign substances are recognized as "nonself." Thus, recognition occurs with resultant mucosal cell stimulation. First, macrophages, DCs, NK cells, and others participate in the initial response. Subsequently, the immunologic response specific for a particular immunogen is then in turn followed by further surveillance (Brandtzaeg 1995; Sanderson and Walker, 1994).

#### Absorption of immunogens

Although the absorptive mechanism into the nasal mucosa has yet to be fully elucidated, there appear to be two alternative routes. One absorption route is intercellular; however, in the normal human, the tight junction between epithelial cells would provide a major barrier for transport of substances (Schneeberger and Lynch, 1992). The second absorption mechanism involves cellular ingestion by endocytosis (*i.e.*, pinocytosis and/or phagocytosis). The magnitude and acceleration of substance absorption, in any case, are intrinsically dependent upon such conditions as the degree of epithelial damage and epithelial permeability. These conditions characterizing absorption may be modulated by proteases, cytokines, eosinophil- and neutrophil-derived proteins, and bacterial products that have been found in the epithelia of the trachea, bronchus, and bronchiolus (Lewis *et al.*, 1995).

#### Primary and secondary immune responses in the nose

Precisely how the primary immune response occurs in the nose remains unknown. Speculatively, however, consideration has been given to the idea that the immunogens derived from either absorbed substances or microorganisms are brought to the nose and the nasal-associated lymphoid tissue (NALT) through the nasal peripheral lymphatic vessels, and result in the induction of a primary immune response. This mechanism may be comparable to the gut-associated lymphoid tissue (GALT) or the bronchus-associated lymphoid tissue (BALT). Immunologic function of the NALT in experimental animal systems has been extensively investigated. The immunogen brought into NALT is engulfed by antigen-presenting cells (APC) (*e.g.*, macrophages and DCs) and activates T and B cells. In humans, M cells have not been observed in nasal and paranasal sinus; in spite of this, a newly developed germinal center in the sinus has been found that exhibits chronic inflammation. The adenoid and its surrounding tonsils may be a candidate for NALT in humans. Supporting evidence for this hypothesis is that T- and B-cell proliferation and differentiation in adenoid and palatine tonsils have

been found in infants 1 year after birth. In the secondary immune response, it has been proposed that the committed T and B cells distribute to the nasal mucosa from the NALT (Phillips-Quagliata and Lamm, 1994) and differentiate into plasma cells. The major Ab isotype is IgA and to a lesser degree IgG, IgM, IgD, and IgE. As supported by evidence that infiltrating T lymphocytes of allergic patients express mRNA for cytokines when challenged with specific antigen (Ag), it has been proposed that cytokines can be produced and are secreted in the nasal mucosa and display immunologic functions in the nose.

## EFFECTORS FOR THE NASAL IMMUNE RESPONSE

#### Nasal secretory antibodies

Nasal secretions are derived chiefly from goblet cells and nasal glands. Exudation of tissue fluid components possibly leak through the epithelial intercellular junction under specific conditions, increasing epithelial permeability. The secretions consist of minerals, enzymes, serum components including Abs, and locally produced substances. Nasal IgA molecules with Ab activity are usually dimerically bound with the joining molecule (J chain) and the cleaved polymeric Ig receptor termed secretory component (SC), as seen for IgA of parotid and intestinal fluid. Microbial IgA immune complexes formed in the nasal secretion bind to lysozyme and are subsequently lysed. Antigen-specific secretory IgA (S-IgA) Abs function locally by binding the antigen and blocking its penetration into the mucosa. A recent study of salivary IgA suggested that high levels of S-IgA may protect sensitized children from developing allergic symptoms during the first 2 years of life (Boettcher *et al.*, 2002). Other Ab isotypes are present in the nasal secretions; however, to a lesser extent. Furthermore, it should be noted that the biologic importance of the minor Ab isotypes is not fully understood. One exception is IgE, which is responsible for provoking allergic rhinitis (see following section).

#### Infiltration of inflammatory cells

Nasal tissues are exposed to open air containing abundant immunogens immediately after birth and are engaged in the immunologic process of inducing localized inflammation. Even in the early stages of inflammation, the copious immunocompetent and inflammatory cells in the nasal mucosa contain macrophages, DCs, T and B lymphocytes (including plasma cells), mast cells, neutrophils, and eosinophils. Later discussion will show how cytokines and chemical mediators are secreted from these cells, possibly modulating the mucosal immune and inflammatory responses. In contrast to cells migrating into the nasal cavity, they likewise migrate out and are suspended in nasal secretions. Aeroantigenic substances may conceivably interact with these migratory cells in suspension to a specific receptor and induce release of cytokines and chemical mediators.

reacting with epithelial cells and nerve endings that occupy the intercellular spaces of the epithelium.

## RHINITIS, SINUSITIS, AND NASAL POLYPS

Rhinitis and sinusitis may be classified as "allergic and non-allergic" as proposed by the International Rhinitis Management Working Group (1994) and by Togias (1993). However, in this chapter, rhinitis and sinusitis will be described as two distinct entities, "infection and allergy."

### Infectious rhinitis and sinusitis

The nasal cavity, as the point of entry into the respiratory tract, is often the first target of invading microbes. Rhinitis and sinusitis caused by viral and bacterial infections are usually nasal/sinus infections by the common cold virus and epidemic influenza. The causes of rhinitis and sinusitis are diverse; however, the most common cause is viral infection secondary to the common cold (Gwaltney *et al.*, 1994). The common cold is the most widespread viral infectious condition and is usually induced by viruses, such as rhino, influenza, adeno, and parainfluenza (RSV) viruses. If the viral infectious process is prolonged or induces serious mucosal damage, bacterial infection ensues. Acute purulent inflammation frequently occurs as a result of secondary bacterial infection, with sinus involvement of the nose following the viral infection. Major causative bacteria of acute rhinosinusitis are *Streptococcus pneumoniae*, *Hemophilus influenzae*, and *Staphylococcus aureus*.

The relationship between infections and allergic disease in the upper respiratory tract has not been well defined, as will be discussed later. The results from studies that have examined the influence of atopy on the development of the common cold are controversial (Bardin *et al.*, 1994; Avila *et al.*, 2000). The effects of the common cold on allergic rhinitis also have not been established. Nasal responses to infections may be different depending upon the species of microbe.

### Infiltration of the inflammatory cells

Inflammatory cells present in the nose and sinus with infection are predominantly lymphocytes and neutrophils (Deacon *et al.*, 1996). Antigenic (Ag) substances derived from microorganisms, including endotoxin, induce immune responses in the nasal and paranasal mucosa resulting in lymphocyte activation and Ab responses. S-IgA (Ab) production with Ag specificity is a major player in the nasal and paranasal mucosa. Furthermore, there are trace amounts of IgG, IgM, and IgE Abs.

Cytokines are produced and released from the activated T lymphocytes, thereby initiating the expression of ICAM-1, VCAM-1, and E-selectin in the endothelial cells of nasal blood vessels. ICAM-1 plays a prime role as an adhesion molecule for neutrophils. It is now accepted that chemoattractants for extravasation of vessel-adhered neutrophils and for endothelial migration into the infected site are bacterial

products, complement components, LTB<sub>4</sub>, PAF, eicosanoids (*e.g.*, 5HETE), and CxC chemokines. Complement components such as C3a, C5a, and C567 complexes have a strong chemotactic activity toward neutrophils, which are activated by the classical complement pathway triggered by IgG/IgM immune complexes and an alternative pathway triggered by IgA immune complexes. PAF, LTB<sub>4</sub>, and 5HETE are released from mast cells and also from macrophages after stimulation via complement receptors on the cell membrane. Intensive studies showed that CxC chemokines such as IL-8 and gro/MGSA have selective chemoattractive activity for neutrophils (Himi *et al.*, 1997; Suzuki *et al.*, 1996).

Although the exact mechanism has not been clarified, neutrophils infiltrate into the mucosa and then migrate farther out to the nasal cavity. These cells have been detected in smears of the nasal secretion from rhinosinusitis patients. It has been well documented that important functions of neutrophils are killing of pathogens by endocytosis and digestion by lysosomal proteases in granules, chiefly by elastase, cathepsin D, and collagenase. Additionally, released or discharged enzymes from the activated neutrophils digest tissue components resulting in pus or purulent secretions with degenerated epithelial tissue components, which hallmark these secretions as infectious rhinosinusitis. However, sinusitis caused by fungal infections exhibits a different etiology; for example, infections by aspergillus, mucol, or candida. Serum Abs to fungi, mainly IgG and IgM, can be detected in most fungal sinusitis cases and even in healthy individuals. However, Ab production in the nasal mucosa has not been well established. Fungal Ags often induce type III and type IV and sometimes type I allergy. Both bacterial and fungal infections develop into a more severe state when patients are immunocompromised, clearly illustrating the contributive powers of immunologic defense to the upper respiratory tract.

### Chronic change of the infectious rhinitis and sinusitis

Chronic changes of infectious rhinitis and sinusitis are caused by prolongation of inflammation, which may be induced by a multitude of factors, such as repeated infection, mediators and cytokines released by the inflammatory cells (Driscoll *et al.*, 1996), and biologic defensive blocking effects of polysaccharides (biofilm) produced by infected bacteria and anatomic conditions. The Task Force on Rhinosinusitis of the American Academy of Otolaryngology—Head and Neck Surgery recommended that sinusitis should be more appropriately referred to as rhinosinusitis to reflect the frequent involvement of the nose. Rhinosinusitis is classified according to duration of symptoms as acute (6 weeks), subacute (6 to 12 weeks), or chronic (12 weeks) (Lanza *et al.*, 1997).

Chronic inflammation is histologically characterized by edema, granulomatous changes (with or without newly developing germinal centers), and subsequent fibrous degeneration. These chronic changes are often seen in the sinus mucosa. The overall character of the secretion is changed in rheologic properties, clearly affecting mucociliary function (Majima *et al.*, 1993). It has been shown that there are some histochemical differences between characteristics of

inflammation induced by microbial infections and type I anaphylactic reactions. Allergic rhinitis has been cited as a risk factor for the development of chronic sinusitis (Wald, 1992; Kaliner *et al.*, 1997; Huang, 2000). Allergic-sensitized mucosae may show stronger inflammatory changes than normal mucosae following infection. In addition, viral infections may enhance allergic inflammation in the nose. Our experimental data showed that nasal RSV infections significantly exaggerated nasal hypersensitivity to histamine and ovalbumin (OVA) in mice sensitized with OVA.

### Nasal polyps

Nasal polyps usually originate around the opening to the ethmoid sinus. The polyps protrude into the nasal cavity, resulting in nasal obstruction, secretion, and loss of smell. Although the prevalence of nasal polyps in the general population has not been well documented, a higher incidence is found in men than women, and in those over 40. Cystic fibrosis should be considered when nasal polyps occur in children younger than 10 years of age (Slaviny, 1997).

The precise mechanisms for development of nasal polyps are still obscure. Nasal polyps develop in patients with either nonallergic or allergic rhinitis and sinusitis, especially during chronic inflammation. The prevalence of nasal polyps in allergic rhinitis is not high and is similar to that in the normal population. Nasal polyps are more common in patients with nonatopic asthma and with aspirin-sensitive asthma (Mygind *et al.*, 2000; Voegels *et al.*, 2001; Bachert *et al.*, 2001; Grigoreas *et al.*, 2002).

There is likely a close association between multiple factors for chronic change of rhinosinusitis and polyp development, such as higher sodium absorption and chloride permeability (Bernstein *et al.*, 1997), and local production of epithelial growth factor (EGF) caused by local release of inflammatory mediators (Coste *et al.*, 1996a, b) and cytokines.

Nasal lavages contain a higher percentage of eosinophils and neutrophils, and higher levels of the cytokine IL-5 (Bolard, 2001), tryptase, histamine, and ECP in patients with, than in those without nasal polyps (Di Lorenzo *et al.*, 2001). Homogenized nasal tissue from patients with nasal polyps contains significantly higher total IgE, IL-5, eotaxin, eosinophil cationic protein (ECP), LTC<sub>4</sub>/D<sub>4</sub>/E<sub>4</sub>, and sCD23 than nonpolyp tissue (Bachert *et al.*, 2001).

The recruitment and activation of inflammatory cells seen in nasal polyps are under the control of cytokines and chemokines such as IL-5, GM-CSF (Jordana *et al.*, 1997), IL-8, eotaxin, and GRO- $\alpha$  (Klein *et al.*, 2000). The damaged epithelium was observed in nasal polyps, where eosinophils contribute to the release of granular proteins. The ongoing process of tissue degradation and remodeling may trigger mechanisms of polyp formation. Growth factors, such as TGF- $\alpha$ 1, TGF- $\beta$ 1 (Elovic *et al.*, 1994), basic fibroblast growth factors (Norlander *et al.*, 2001), PDGF, and FGF (Silvestri *et al.*, 2002), stimulate the proliferation of fibroblasts, endothelial cells, and glandular epithelium (Kimura *et al.*, 2002) and may contribute to local thickening of the basal membrane, stromal fibrosis, and epithelial hyperplasia.

The expression and activation of the growth factors are influenced by proinflammatory cytokines, such as IL-1 $\beta$ , IL-6, and IFN- $\alpha$ . Fibroblasts are a major source of extracellular matrix proteins and are rich in cyclooxygenases (Lin *et al.*, 2002), by production of prostaglandins, which lead to vascular permeability and influence cytokine production. In addition, the denervation observed in polyp stroma may induce an abnormal vascular permeability and contribute to tissue edema.

In the case of aspirin-tolerant patients, Cox1 and Cox2 expression was found in nasal polyps (Mullol *et al.*, 2003). This finding suggests that prostanoid metabolism may be important in the pathogenesis of inflammatory nasal diseases and plays a potential role for this alteration in the formation of nasal polyps (Mullol *et al.*, 2002). Taken together, increased release of inflammatory mediators contributes to the development of nasal polyps, determining edema and an increased recruitment of inflammatory cells.

Nasal polyps may be histologically classified into three types: edematous, fibrous, and glandular with cystic changes and cell-rich granulomatosa (Jordana *et al.*, 1995). These histologic patterns are seen in both infectious and allergic polyps; however, polyps in infectious rhinosinusitis are of granulomatous and fibrous types in higher frequency when compared to those in allergic rhinosinusitis. This is likely due to a relatively strong inflammation and subsequent inflammatory degeneration that occurs in the chronic infectious state. However, allergic inflammation is characterized histologically by edematous thickening of the nasal and paranasal sinus mucosa indicating a local anaphylactic reaction, which may be histologically reversible.

### Allergic rhinitis and sinusitis

Major symptoms of allergic rhinitis and sinusitis are sneezing attacks and nasal hypersecretion and obstruction, which are triggered by IgE-mediated anaphylactic reactions and inflammation of the nose generated by inhaled allergens.

### Allergens that induce allergic rhinitis

Causative allergens for allergic rhinitis are primarily inhaled aeroallergens, such as tree pollen, grasses and weeds, fungal products, and house dust (domestic) mites, and mammalian-derived allergen, such as cat and dog dander (Table 87.1) (Stewart and Thompson, 1996; Naclerio and Solomon, 1997). Many of the responsible allergens have already been chemically defined in terms of Ag size and epitope sequence.

### Cell recognition of allergen

The T-cell receptor (TCR) response against Ag epitopes of allergens such as pollen, house dust mites, and others has been extensively investigated over the past decade (Ebner *et al.*, 1993; Ikagawa *et al.*, 1996; Schenk *et al.*, 1995; Spiegelberg *et al.*, 1994; van Neersen *et al.*, 1994; Yssle *et al.*, 1992). It has generally been thought that allergenic epitopes are recognized by helper T (Th) cells as peptides of a particular amino acid sequence, which combines with human leukocyte antigen (HLA) complex class II molecules.



Table 87.1. Major Inhaled Allergens Causative to Allergic Rhinitis

Common Name	Scientific Term	Abbreviation for Purified Antigen
<b>Grass pollen</b>		
Orchard grass	<i>Dactylis glomerata</i>	Dac g1,2,5
Rye grass	<i>Lolium perenne</i>	Lol p1-5,10,11
Timothy grass	<i>Phleum pratense</i>	Phl p1,2,5,6
Bermuda grass	<i>Cynodon dactylis</i>	Cyn d 1
<b>Weed pollen</b>		
Short ragweed	<i>Ambrosia artemisiifolia</i>	Amb a1-3,5-7,10
Giant ragweed	<i>Ambrosia trifida</i>	Amb t5
Western ragweed	<i>Ambrosia psilostachya</i>	Amb p5
Mugwort	<i>Artemisia vulgaris</i>	Art v1,2
<b>Tree pollen</b>		
Birch	<i>Betula verrucosa</i>	Bet v1-3
White oak	<i>Quercus alba</i>	Que a1
European chestnut	<i>Castanea sativa</i>	Cas s1
Apple		18KD
Olive	<i>Olea europaea</i>	Ole e1,2
Japanese cedar	<i>Cryptomeria japonica</i>	Cry j1,2
Cypress	<i>Cyprinus carpio</i>	42kD
<b>House dust mite</b>		
<i>Dermatophagoides pteronyssinus</i>		Der p1-9 (Der p1:cysteine protease)
<i>Dermatophagoides farinae</i>		Der f1-3,6,7,10, 67kD (Der f1:cysteine)
<b>Insect allergen</b>		
German cockroach	<i>Blattella germanica</i>	Bla g1,2,4,5
<b>Animal and dander</b>		
Cat	<i>Felis domesticus</i>	Fel d1, chain 1
Dog	<i>Canis familiaris</i>	Can f1,2
<b>Fungal allergen</b>		
	<i>Alternaria alternata</i>	Alt a 1,2,6,7,10, 70kD
	<i>Aspergillus fumigatus</i>	Aspf 2

Subsequently, the T cell accepts the cognate Ag signal with a specific HLA molecule and undergoes activation with release of cytokines. The production of IgE Abs is regulated by the Th2-type cytokine network, which includes IL-4, IL-5, IL-6, and IL-13. As mentioned previously, secondary immune responses involving IgE Ab formation could occur in both NALT and the nasal mucosa. In this regard, it has been reported that when allergic patients are nasally challenged and provoked by the responsible allergen, lymphocytes infiltrating the nasal cavity produce Th2-type cytokines (Durham *et al.*, 1992).

#### Genetic factors regulating allergic rhinitis

In the concept of "atopy," which was defined by Coca and Cooke (1923), genetic factors were given importance in regulation of hay fever and asthma. Family studies have confirmed that asthma and hay fever are based upon

immunologic responses with a hereditary cause (Coca and Cooke, 1923; Edford-Lubus, 1971). However, it is certain that there are multiple genetic factors relating to each step of this chain reaction from Ag sensitization to manifestation of symptoms. The primary target of genetic studies has been of individual differences in IgE responsiveness to a specific allergen. Association of disease to HLA type, in which expression is regulated by genes mapped on chromosome 6p, has been extensively studied. Pedigree analysis of Japanese cedar pollinosis indicated that allergic rhinitis shows HLA haplotype linkage (Sasazuki *et al.*, 1984). Statistical analysis of HLA allele frequency has been studied with the population allergic to a certain allergen, such as ragweed pollen, house dust mites, Japanese cedar pollen, cat dander, rye grass, birch pollen, and others (Marsh *et al.*, 1992; Matsushita *et al.*, 1987; Sadanaga *et al.*, 1990). The HLA phenotype association to its allergy may depend upon



the HLA molecule restricting specific recognition of each associated allergen epitope and to the difference between high and low responders against a certain allergen. However, Cookson *et al.* (1989, 1992) reported that IgE Ab responses underlying asthma and rhinitis were linked to chromosome 11q. It has also been reported that production of IL-4 cytokine and IgE Ab molecules (not associated to antigen specificity) is regulated by the gene mapped on 5q31.1 (Marsh *et al.*, 1994).

The next step in the cascade of allergic reactions involves binding of IgE Abs to the mast cell via FcεR1 thereby showing this to be the key event for mast cell sensitization. Others have reported that a gene on chromosome 11q regulates FcεR1 expression (Shirakawa *et al.*, 1994). Taken together with IgE Ab responses regulated by chromosome 11q, as described earlier, 11q may map important genes through its regulating "atopic disposition."

The final effector event is the reactivity of target tissues, such as the smooth muscle of blood vessels, glands, and nerves, to appropriate chemical mediators. There is a significant possibility that receptor-directed reactivity to chemical mediators, like histamine, leukotrienes, platelet-activating factor (PAF), and even neuropeptides may be genetically regulated. The gene for expression of β2 adrenergic receptor maps to 5q31-33, which is closely located to IL-4 and IgE receptor genes (Postma *et al.*, 1995) as described earlier and

which are possibly associated with asthmatic reactions. Most studies now indicate that allergic rhinitis is genetically controlled; however, the genetic factors are quite complicated as a result of their genetic polymorphism, Ag variety, and multiple reaction steps in the allergic response. Therefore, investigations into the comprehensive functional chromosome-to-chromosome network will be an important future target for investigations seeking a regulatory mechanism for allergy.

**The effector phase of allergic inflammation in the nose**

The mechanism of effector reaction of nasal allergic inflammation is outlined in Figure 87.1, although there are still several areas to be clarified to complete the reacting cascade.

**Local anaphylaxis**

IgE Abs produced in the nose by the local immune response against inhaled and absorbed allergen sensitize the infiltrating mast cells by binding to FcεR1. The secondary Ag challenge forms IgE-allergen complexes on the mast cell membrane and induces release of stored and newly synthesized chemical mediators, which then bind to mediator receptors on target tissues, such as nasal blood vessels, glands, sensory nerves (trigeminal), and epithelial cells. A major mediator, histamine, reacts to the H1 receptor of

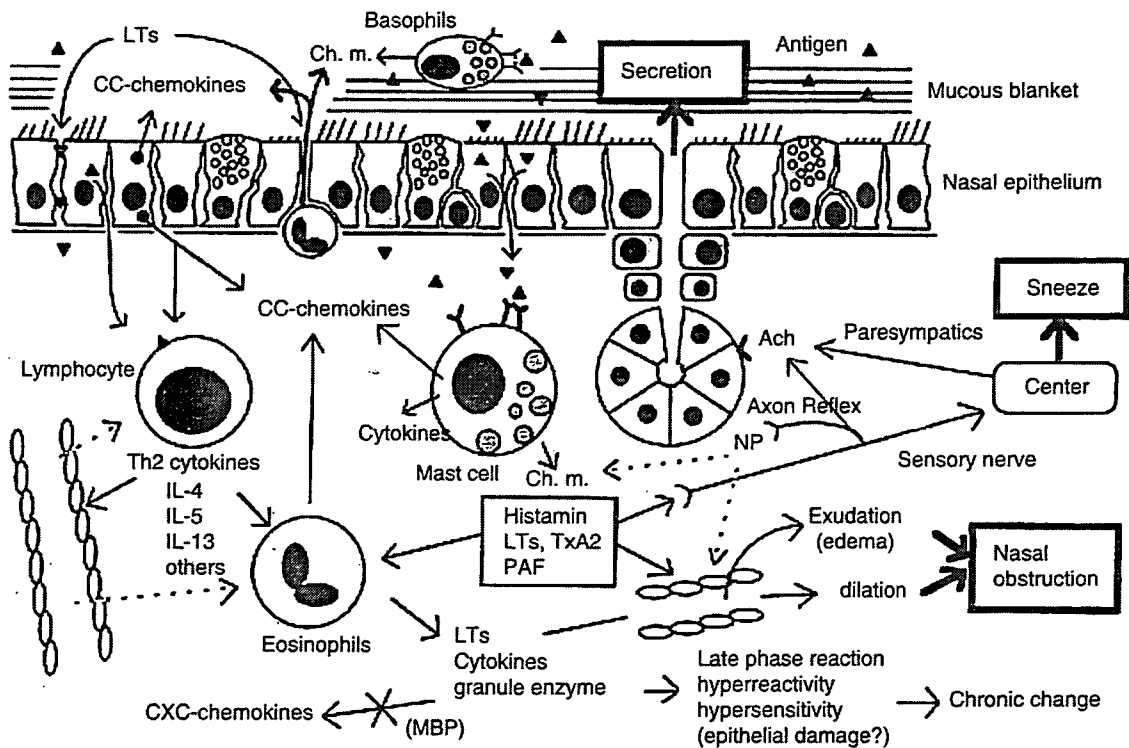


Fig. 87.1. Effector reaction cascade of nasal allergic inflammation. The scheme demonstrates a reaction cascade in nasal mucosa provoked by antigen challenge. This reaction proceeds to cellular, vascular, glandular, and nervous reaction, resulting in typical symptom manifestation of nasal anaphylaxis and allergic inflammation. The precise process of the effector reaction is described in the text. LT, leukotrienes; TxA2, thromboxane A2; Ch.m., chemical mediators; MBP, major basic protein; PAF, platelet-activating factor; NP, neuropeptide; Ach, acetylcholine.

trigeminal nerve endings and stimulates the sneeze reflex processed in the superior salivary nucleus. This impulse is transmitted to efferent parasympathic nerves innervating peripheral nasal endings resulting in the release of acetylcholine. This release reacts primarily with the cholinergic receptor of the nasal gland, hence inducing a nasal secretion. Nasal obstruction is manifested by an increase in the nasal mucosal volume created by blood vessel dilation. This is probably induced by leukotrienes, histamine, nitric oxide, neuropeptides (including substance P, CGRP, VIP, and acetylcholine), and  $\beta$  adrenalin. Another nasal obstruction mechanism is edematous change of the nasal mucosa caused by an increase in blood vessel permeability, which is mainly provoked by chemical mediators, such as histamine, leukotrienes, thromboxane A<sub>2</sub>, and PAF. These resulting symptoms, and their related chain reaction caused by allergic rhinitis, are chiefly characterized by allergen-IgE-mast cell reaction axis, and are defined as "local anaphylaxis."

#### Late phase reactions, hyperreactivity, and hypersensitivity

A single Ag challenge provokes an immediate anaphylactic reaction in the nasal mucosa within 5 to 15 minutes, and the duration of the symptoms may be shorter than 1 hour. In 10% to 20% of the cases, the symptoms, mainly nasal obstruction, occur again 5 to 10 hours after the Ag encounter. This phenomenon is called "late phase reaction of allergic rhinitis," which is comparable to the late asthmatic symptom. Responsible mediators are considered to be leukotrienes, thromboxane A<sub>2</sub>, histamine, and ECP. Multiple and continuous antigen challenge may induce hyperreactivity to histamine, acetylcholine, and other irritants (Andersson and Mygind, 1995). Histamine sensitivity is significantly increased in patients with allergic rhinitis as compared with normal individuals when a series of concentrations of histamine are applied to the nasal mucosa. Although the continuous stimulation of mediators or cytokines (derived from inflammatory cells) and neuropeptides may also cause hyperreactivity to be provoked (Konno *et al.*, 1996), there are no reports of direct evidence, to date, that these factors do enhance expression of histamine or acetylcholine receptors on the target tissue in humans. Our laboratory showed that H1 receptor expression on rat trigeminal ganglion is enhanced by PAF stimulation. However, the experiment could not be extended to humans.

Cytokines and mediators from epithelial cells may also contribute to induction of hypersensitivity (Hulsmann and De Jongste, 1996). Hyperreactivity and hypersensitivity against chemical irritants, temperature, and other factors have been generally understood to be caused by naked sensory nerve endings resulting from eosinophil-induced epithelial damage. As others have noted, however, the relationship between airway epithelial damage and airway hyperresponsiveness cannot be easily attributed to one of the putative mechanisms (Hulsmann and De Jongste, 1996). In our studies, there was no clear and conclusive evidence that eosinophils injure the nasal epithelium.

#### Inflammatory cell infiltration into allergic nasal mucosa

##### Mast cells

The mast cell is undisputedly the star player of the IgE-allergen anaphylactic reaction axis (Befus, 1994; Church and Levi-Schaffer, 1997). Generally, mucosal mast cells are found in higher frequency in the shallow portions of the nasal mucosa, beneath the epithelial lining, whereas connective tissue mast cells are distributed in the deeper layer. Supportive data highlight these findings: 80% of basophilic cells in a scraped sample of the nasal mucosa were stained by alcian blue-safranin and were tryptase positive, indicating that most of basophil-type cells in the sample were actually mucosal mast cells (Hastie *et al.*, 1979; Okuda, 1987; Otsuka *et al.*, 1985). Therefore, it is possible for nasal mucosal mast cells to react with the inhaled allergen in the shallow layer of the mucosa and to release chemical mediators. The released mediators may react with epithelial cells and increase their permeability, which in turn may stimulate the intercellular innervated sensory nerve endings. Basophils in nasal secretions (widely known as IgE target cells), however, increase in number after nasal antigen provocation. However, those basophils contain appreciably lower amounts of histamine than mucosal mast cells (Okuda *et al.*, 1992). This may demonstrate that mucosal mast cells are considerably more concerned with effectors of allergic rhinitis than are basophils.

##### Lymphocytes

The homing mechanism of committed lymphocytes has not been thoroughly explained in the nose. However, it is certainly inarguable that lymphocyte infiltration is of great importance in the nasal mucosa with regards to allergic rhinitis. The phenotype of infiltrating lymphocytes are dominantly CD8<sup>+</sup> in the epithelial layer and CD4<sup>+</sup> in the lamina propria. TCR analysis indicated that TCR $\gamma\delta$  cells are found only in the epithelial layer and TCR $\alpha\beta$  cells only in the lamina propria (Okuda, 1992). However, the biologic importance of this segregation has remained unclear (Takeuchi *et al.*, 1997). It is commonly agreed that Th2-type cytokines are key elements in allergic inflammation. Others have reported that T lymphocytes in the nasal mucosa of patients with allergic rhinitis with specificity for timothy pollen express predominantly mRNA for Th2-type cytokines, such as IL-4 and IL-5 (Durham *et al.*, 1992). Following this specific Ag challenge in the nose, the IL-4 and IL-5 expression, but not IL-2 or IFN- $\gamma$ , is consequently enhanced in T lymphocytes and mast cells of tissue samples taken 24 hours after the challenge (Ying *et al.*, 1994). Pretreatment with a nasal topical steroid inhibited the expression of mRNA for Th2-type cytokines (Masuyama *et al.*, 1994; Rak *et al.*, 1994). In fact, repeated allergen challenge induced significant IL-4 and IL-5 secretion. IL-4 is well known as an important cytokine not only for B-cell isotype switching to IgE but also for induction of expression of adhesion molecules (VCAM-1, ICAM-1) on endothelial cells of blood vessels. Additionally, IL-5 is an important cytokine for IgA-B cell differentiation and eosinophil differentiation and propagation. Therefore, both

IL-4 and IL-5 are closely related factors in eosinophil infiltration and function and are accordingly essential cytokines for positive effectors of allergic inflammation along with additional Th2-type cytokines, such as IL-3, IL-6, and IL-13.

### Eosinophils

Eosinophil accumulation in the nasal mucosa and in external secretions is a major diagnostic criterion for allergic rhinitis. The mechanism of the infiltration is most evident, with only a few missing elements required to complete the reaction chain. Chemoattractants for eosinophils are considered to be PAF, LTB<sub>4</sub>, IL-5, and CC chemokines, as seen when allergic inflammation in the nasal mucosa is evident. One study focused attention on RANTES, eotaxin, and monocyte chemoattractant protein-3 (MCP-3) as being the most relevant CC chemokines (Terada *et al.*, 1996; Teran and Davies, 1996). Specific selectivity of chemoattractant activity for eosinophils was associated with both eotaxin and RANTES. Eotaxin occurs in the bronchial epithelium, endothelial cells of blood vessels, and epithelial cells of nasal polyps. Nasal epithelial-derived eotaxin will raise a special interest because of its selective recruitment of eosinophils. Further studies of eosinophils have shown the selective adhesion molecule VCAM-1 to be another important factor for infiltration of eosinophils into the nasal mucosa. When eosinophils adhere and selectively stop on endothelial cells of the blood vessel, chemoattractants reacting with both neutrophils and eosinophils appear to allow for preponderance of eosinophils. However, as is often observed, eosinophil accumulation in the nasal secretion from allergic rhinitis is so selective that more than 80% of cells in the secretion are eosinophils. To explain this high specificity, a blocking process may occur thereby inhibiting neutrophil mobility with the eosinophil recruitment in parallel to its role as a specific adhesion to endothelial cells and the eosinophil attractants. Antiheparin activity of major basic protein (MBP) from eosinophils may inactivate Cx<sub>2</sub>C chemokines, which are known neutrophil attractants. It has been proposed that asthma may also be defined as a desquamative eosinophilic bronchitis. However, in the case of allergic rhinitis, there are diverse opinions surrounding the tissue damage theory, because the epithelial cell damage of the nasal mucosa is not remarkable when observed under light microscopy. Electron microscopic examination revealed eosinophil migration through intercellular spaces in animal models and in humans (Fig. 87.2A). Thus, the normal tight cell-to-cell junction is disengaged for the purpose of opening a passage for the eosinophil migration (Schneeberger and Lynch, 1992). Tight junction arrangement of nasal epithelium was morphometrically analyzed under freeze-fracture examination and comparative view between DNP-challenged and unchallenged guinea pigs passively sensitized with anaphylactic Abs to DNP. Insignificant differences in strand arrangement were found in both experimental groups (Samejima *et al.*, 1988) (Fig. 87.2B). Nevertheless, tight junctional strands of the challenged group showed a slight decrease when compared with a control group. There were no defective strands. This

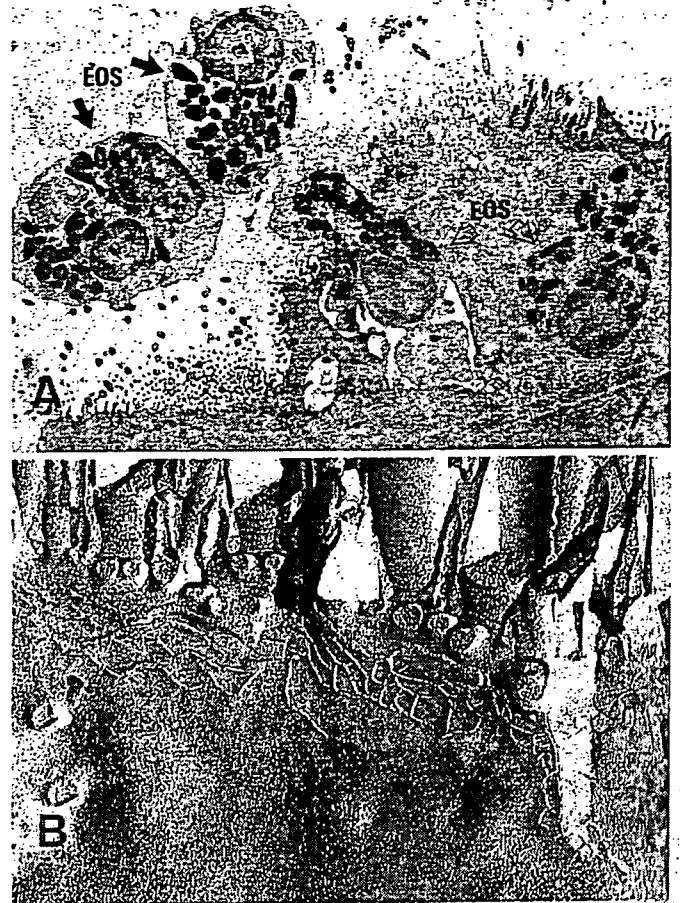


Fig. 87.2. Electron micrograph of eosinophil transepithelial migration and nasal epithelial tight junction in an allergic animal model. A, Nasal antigen challenge to passively sensitized guinea pig by DNP-anaphylactic antibodies produced predominant eosinophil transepithelial migration. B, A freeze-fracture electron micrograph of apical membrane of the Ag-challenged nasal epithelium demonstrates clear shape of tight junction strands; however, arrangement and number of strands did not show marked changes in the Ag-challenged experimental animal group when compared with the unchallenged group. EOS, eosinophils.

indicates that epithelial damage by eosinophil infiltration may be considered insignificant in the nasal mucosa. Accordingly, it may be important to further study eosinophil function from the perspective that they may function as an initiator for remodeling of allergic inflammation.

### Allergic sinusitis

Examination of paranasal sinuses by x-rays has been performed in 335 cases (189 male and 146 female, average age  $21.8 \pm 14.2$  years) who have typical symptoms of allergic rhinitis without purulent nasal discharge and whose responsible allergens have been identified by skin test, IgE RAST, and nasal provocation test. Approximately 40% of the subjects showed sinus shadow. About 70% of these were polypous and mucosal thickening type (Fig. 87.3) (Sumell *et al.*, 1993). Histologic analysis of typical cases indicated abundant eosinophil infiltration, edematous and polypoid

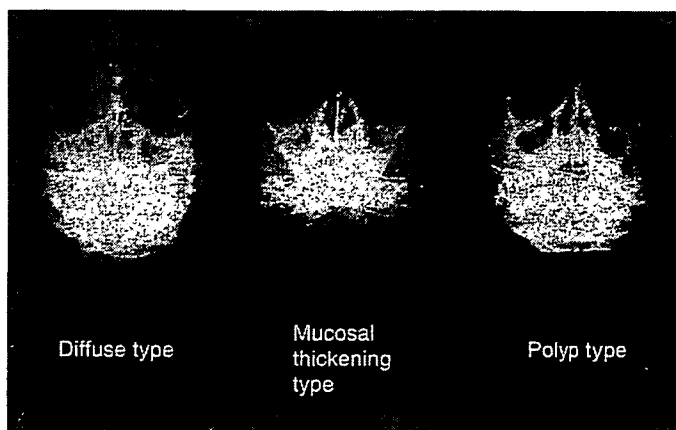


Fig. 87.3. Waters radiographic view of a patient with allergic and/or infectious rhinosinusitis. Types of shadow demonstrated in the picture are diffuse, mucosal thickening, and polyp. Relatively higher incidence of mucosal thickening and polyp type are seen in patients with allergic rhinitis. The diffuse type is found frequently in cases with infectious rhinosinusitis.

changes with increases in goblet cells, and thickening of the epithelial basement membrane, which are obviously comparable findings to nasal mucosa with allergic rhinitis. Eosinophils in the paranasal mucosa are significantly lower (density and EG2 positive, suggesting that they are in an activated state (Ogata *et al.*, 1997). However, several patients with sinus shadow also have neutrophil infiltration comparable to eosinophils in the nasal secretion, suggesting that allergic and bacterial inflammation could coexist in those cases, especially in children. Others have reported that inoculation with *Streptococcus pneumoniae* induced significant sinus inflammation in allergic mice sensitized with OVA, as indicated by neutrophil, eosinophil, and mononuclear influx into the sinus mucosa (Blair *et al.*, 2001). The results suggested that allergic inflammation enhances bacterial sinusitis. As described previously, on the contrary, viral infection in the nose may exaggerate local hypersensitivity against histamine and allergens. Therefore, either allergy or infection could trigger induction and enhance the sinusitis combined with infection and allergic inflammation. The incidence of developing allergic polyps in the paranasal sinus is higher than in the nasal cavity, although the reasons for this remain unknown. The relationship between allergic sinusitis and asthma may be important for both present and future research.

#### Immunotherapy

The general acceptance has been that allergen-specific immunotherapy is effective on perennial and seasonal allergic rhinitis (Bousquet and Michel, 1995; Malling and Weeke, 1994). Conventional immunotherapy performed by either subcutaneous or intranasal application of allergen does not result in significant suppression of IgE Ab production in clinical trials. It has been shown that indicated successful grass pollen immunotherapy is associated with inhibition of seasonal increases in basophils and eosinophils in the nasal

biopsy specimens (Wilson *et al.*, 2001). Others reported that allergen-specific immunotherapy increased the numbers of nasal mucosal cells expressing mRNA for the Th1-type cytokine IFN- $\gamma$  in the successful cases (Durham *et al.*, 1996). Furthermore, a 3-year period of immunotherapy decreased the numbers of cells expressing IL-4 mRNA and suppressed late phase reactions in the skin. Those effects lasted for 3 years even after the cessation of the injection of allergen (Durham *et al.*, 1999). Others found that preseasonal grass pollen immunotherapy for 3 years was clinically effective in 5- to 16-year-old children, which effects still benefit significantly in 6 years after discontinuation of the immunotherapy (Eng *et al.*, 2002). Another group indicated from the results of a randomized study using 205 children aged 6 to 14 years that pollen immunotherapy for 3 years reduced the development of asthma in children with seasonal rhinoconjunctivitis (Moeller *et al.*, 2002).

These data suggest that the allergen-specific immunotherapy has the potential to modify the natural course of allergic diseases. In the past decade, chemical analysis of allergen epitopes has seen rapid progress. Using synthetic peptides in accordance with the amino acid sequence of the allergen, TCR recognition system is being extensively studied with the aim of clinical therapeutic applications (Sloan-Lancaster *et al.*, 1993). The T-cell epitope for an allergen does not induce an anaphylactic reaction in patients to the given allergen. Collaborating this fact, it has been reported in animal models that direct reactions of the T-cell epitope and the TCR without participation of costimulatory factors actually induces tolerance. A target for the study has been to ascertain if allergen-specific tolerance and/or anergy could be induced in human subjects. In contrast, the TCR response produces various cytokines of Th0, Th1, or Th2 cell origin and is restricted by the HLA phenotype of an individual, which is, of course, genetically determined. The complicated findings that have been provided in this area give strong impetus to searching for Th1-dominant modulation in human trials by peptide immunotherapy. Clinical trials of peptide immunotherapy using synthesized Fel dI fraction of cat dander has now been done (Briner *et al.*, 1993; Marcotte *et al.*, 1998). Cry j1 and Cry j2 are known to be major allergen components of Japanese cedar pollen (JCP), which induces severe symptoms of rhinoconjunctivitis in a large Japanese population. T-cell epitopes in allergen peptides derived from JCP have been extensively analyzed for clinical application as nonanaphylactogenic therapeutic allergen peptides (Ishikawa *et al.*, 1997; Sone *et al.*, 1998; Sone *et al.*, 1999; Hirahara *et al.*, 2001; Taniguchi, *et al.*, 2001). Others have synthesized chemically combined allergen peptides named "Cry-consensus" that consist of two peptides from Cry j1 and three from Cry j2 (Sone *et al.*, 1998). The consensus is nonanaphylactogenic and may be useful for management of patients with JCP having various types of HLA class II molecules. On the other hand, the engineered allergen, in which the disulfide bond that linked the N- and C-terminal sequences of major house dust mite antigen, Der f2, was disrupted, retained T-cell epitopes essential for

immunotherapy and an ability to stimulate T-cell proliferation (Takai *et al.*, 1997). Such engineered allergens are nonanaphylactogenic and may be potentially useful for more effective immunotherapy.

The pharmacologic efficacies of humanized mouse monoclonal Abs to IgE CH3 are neutralization of free IgE molecule, suppression of IgE production, and downregulation of FcεR expression on mast cells and basophils (Chang, 2000), which are supported by the results of multiple phase II and III human clinical studies of asthma and allergic rhinitis, including pollinosis (Christoph and Jardieu, 1997). Our group tried recently to treat patients with Japanese cedar pollinosis, resulting in its potential clinical effect when compared with a placebo control. Safety and efficacy of other routes of immunotherapy than subcutaneous injection of allergen, such as oral, sublingual, nasal, or bronchial routes, have not been well established. However, the allergen immunotherapy performed by nasal (Mestecky *et al.*, 1994) or sublingual routes (Malling 1996; Frew and Smith, 2001) may be worthwhile clinical trials to induce local mucosal immune responses to either the allergen-specific tolerance or a Th1-dominant condition. Our present and established nasal mucosal immunologic knowledge can now afford us this tremendous opportunity.

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# アレルギー性鼻副鼻腔炎

増山敬祐

## はじめに

日本では1970年代頃から花粉症や喘息などのアレルギー疾患が増加している。その1つの要因として、乳児を取り巻く衛生環境が1970年代に激変したことが、その当時出生した人たちのアレルギー発症の増加と関連していると推測されている。実際、1950年～2000年の乳児死亡率の推移を観察すると、欧米はなだらかな減少に対し、日本では1970年代に入り急激な減少を示しているのである。このような衛生環境の急激な変化に対応するかのように、生体側の免疫応答も微妙に変化してきていると考えられるのである。

その根拠ともいえる衛生環境仮説 hygiene hypothesis が今ホットな話題となっている。臨床疫学の伝統ある英国から出されたその仮説では、枯草熱などのアレルギー疾患保有率と関連が強い要因は年長の同胞の数であることが示され、アレルギー保有率はその数に反比例することが明らかにされた。すなわち、非衛生的に年長児から感染を受けることによりアレルギー疾患の発症が防がれるのではなかと考えられた。その後、感染症とアトピー素因やアレルギー疾患発症との関係が多数詳細に検討された。例えば、Shirakawaらは、ツベルクリン反応の程度がIgE抗体の陽性率やアレルギー性鼻炎の発症に逆相関することを報告し、結核菌が宿主の免疫応答をTh2からTh1に変容させうる可能性を示した。

本稿は衛生環境仮説を概説するものではないのでそれは他に譲るとして、上気道である鼻副鼻腔領域においても、蓄膿症などの感染症が減少を示しアレルギー性鼻炎などのアレ

ルギー疾患が増加しているとみて間違いないだろうと思われる。そこでアレルギー性鼻副鼻腔炎である。哺乳類の副鼻腔は生存に必要な機能を補完するために進化をとげたと考えられているが、もともと鼻腔から発生したものであり、ヒトでは単なる含気腔となっているがそもそも鼻副鼻腔として1つの器官として捉えるべきものであろう。したがって本稿においては鼻副鼻腔炎という用語を使用していくことにする。次に、慢性鼻副鼻腔炎について概説する。

## 慢性鼻副鼻腔炎

慢性鼻副鼻腔炎の成因としては従来より感染が知られていた。すなわち、ウイルス感染に続く肺炎球菌やインフルエンザ菌などの細菌感染により、鼻副鼻腔の粘膜腫脹や分泌亢進が起こり、副鼻腔の自然口（上顎洞、篩骨洞、前頭洞の自然口は中鼻道に開口し ostiomeatal complex (OMC) を形成している）が狭くなり閉塞し、洞内の換気不全が生じる。洞内の換気不全は炎症をさらに悪化させ、粘膜内に浸潤した好中球などの炎症細胞により組織障害が惹起され、粘液線毛輸送機能 (mucociliary function) が低下する。また、浸潤炎症細胞からは各種メディエーター、サイトカインが放出され炎症はさらに増悪していく。このようなOMCの狭窄・閉塞と急性炎症の反復には、鼻中隔彎曲症などの局所の解剖学的要因あるいは栄養・生活環境要因などが複雑に絡みあい、慢性の炎症病態（化膿性副鼻腔炎）が形成されていき、重症になると鼻茸も出現していくものと考えられている。

しかしながら、近年、先に述べた衛生環境要因の変化とも相まって、鼻副鼻腔領域に

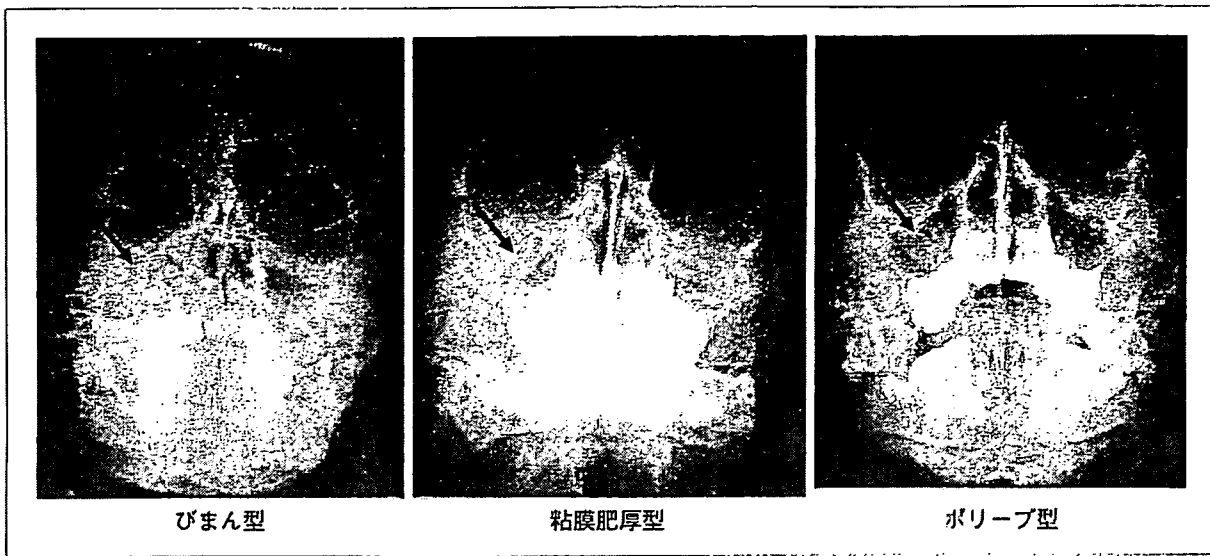


図1 上顎洞陰影の3型

においても感染を契機とした化膿性炎症の減少傾向が認められ（小学校の健診ではいわゆる蓄膿症が激減しアレルギー性鼻炎が著増している）、変わってアレルギー性炎症が目につくようになった。このことは、副鼻腔における炎症病態にも当然影響を与えうることは想像に難くない。

**アレルギー性鼻副鼻腔炎**

アレルギー性鼻炎には副鼻腔炎を合併することが以前より知られていた。いわゆるアレルギー性鼻副鼻腔炎である。しかしながら、これがどのような病態なのか従来より議論のあるところでもある。だが、少なくともその根底にはアレルギー性鼻炎の存在が必須であろうことは疑いがないといえる。したがって、アレルギー性鼻副鼻腔炎の定義としては、アレルギー性鼻炎症状を有し、アレルギーの検査でIgE抗体の関与があり、画像的には副鼻腔に陰影を認めるものと理解される。しかしながら、臨床的には様々な病態を包含しており以下解説する。

**アレルギー性鼻炎に伴う副鼻腔陰影**

X線検査における副鼻腔陰影、特に上顎洞の陰影出現率については、わが国ではいくつ

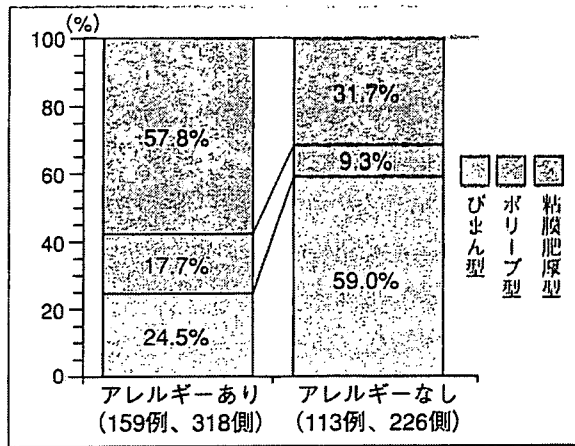


図2 アレルギーの有無による上顎洞陰影

かの報告がみられる。関根、鮫島、分藤ら、石川の報告があり、まとめると35～67%、欧米でも Mygindら（40%）、Naclerioら（60%）が報告しているが同じような比率でみられる。

上顎洞にみられる陰影の型をアレルギー性（アレルギー性鼻炎を有し膿性の鼻汁を認めないもの）と化膿性で比較してみた。上顎洞にみられる陰影の型は、びまん型、粘膜肥厚型、ポリープ型に分類して検討すると、アレルギー性では、化膿性と比較して粘膜肥厚型（58%）やポリープ型（18%）の占める割合が高く、一方、化膿性では59%がびまん性陰影であった（図1、図2）。画像的にも両者には違いがみられるということである。

## アレルギー性鼻副鼻腔炎の病態

それでは、アレルギー性鼻副鼻腔炎はどのようにして発症していくのであろうか。その発症の機序について若干の考察を述べる。

アレルギー性副鼻腔炎は先にも述べたごとく、IgEを介した炎症が鼻腔に起こっていることが前提となる。しかしながら、そのときに併発する副鼻腔炎の発症機序は臨床的には様々な場合が想定できる。ここでは狭義と広義のアレルギー性副鼻腔炎とに分けて論じたい。まず、狭義のアレルギー性副鼻腔炎であるが、これはI型アレルギー反応が副鼻腔でダイレクトに（抗原が副鼻腔に直接入る）あるいはインダイレクトに（血行性に副鼻腔に入る）惹起されて起こる可能性である。次に、広義のアレルギー性副鼻腔炎である。これでは、鼻腔に起こったアレルギー性炎症が副鼻腔に波及する、副鼻腔自然孔の閉塞により二次的な反応が副鼻腔に起こる、神経反射あるいは神経原性炎症が何らかの機序で起こる、副鼻腔に感染が合併しているなどが想定されるのである（表1）。この中で、I型アレルギー反応（狭義）、自然孔閉塞（広義）、感染（広義）について考察する。

## I型アレルギー反応による副鼻腔炎

ダニ抗原に感作されたアレルギー性鼻副鼻腔炎の患者で、手術時に上顎洞粘膜をダニ抗原ディスクで誘発しI型アレルギー反応の有無を病理組織学的に検討した。誘発10分後に粘膜を採取し非誘発部位と比較すると、誘発部位ではマスト細胞の脱顆粒と好酸球の血管内集簇の所見が観察された（図3）。したがって、I型アレルギーが副鼻腔でも起こる可能性があると考えられる。

さらに、副鼻腔に抗原が直接入って抗原抗体反応が起こる可能性については、副鼻腔モデルを使った実験がある。このモデルでは自然孔を介して上顎洞に入る粒子は0.5-0.7mmのものが多いが、5mm以上の粒子は自然孔内径が1.6mmで2%、4.3mmで5.5%入るとされている。通常のダニや花粉抗原

表1 アレルギー性鼻副鼻腔炎の病態

狭義	<ul style="list-style-type: none"> <li>● 副鼻腔自然孔經由に抗原が侵入</li> <li>● 血行性に抗原が侵入</li> </ul>
広義	<ul style="list-style-type: none"> <li>● 鼻粘膜アレルギー炎症の波及</li> <li>● 自然孔閉塞→線毛機能障害→粘液貯留</li> <li>● 神経原性炎症</li> <li>● 感染の合併</li> </ul>

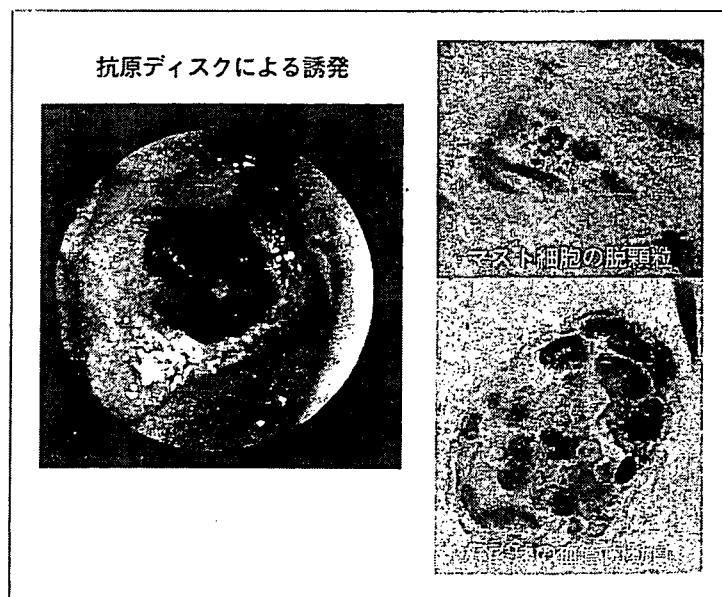


図3 上顎洞粘膜での抗原誘発試験

サイズはこれより大きく実際には入りにくいものと思われるが、5mm以下の断片化した抗原粒子の存在も報告されており、これらのものによる上顎洞内への侵入も十分起こりうると考えられる。実際の患者を対象とした検討も行われている。Slavinらは、ブタクサ花粉症患者5名（副鼻腔は正常）について花粉飛散期の上顎洞の血流と骨代謝の変化をSPECT, PETを用いて検討したが、特に変化を認めなかったと報告した。一方、Pelikanらは、副鼻腔に陰影を認めている症例に鼻腔に抗原誘発を行い、鼻腔での反応（鼻閉を鼻腔通気度で評価）が認められなかった5例にも上顎洞の粘膜肥厚が認められたとしている。血行性に抗原の侵入が起こった可能性も否定はできない。今後とも臨床的検討を重ねる必要がある。

#### 自然口閉塞

黒野らは、鼻中隔彎曲症の診断にて鼻中隔矯正術を施行した患者を対象に以下の検討を行った。術後3日間両側鼻腔にガーゼパッキングを行い、そのときの上顎洞X線陰影を術前のそれと比較し、上顎洞陰影の出現率と出現陰影のパターンを検討した。結果は、約半数に上顎洞に何らかの陰影が現れ、そのうちの半分には粘膜肥厚型の陰影が認められたという。これは先に述べたアレルギー性鼻炎

に伴う副鼻腔陰影のパターンと類似していることが分かる。彼らはさらに、上顎洞内の酸素分圧を測定し、陰影が存在する側では正常側より有意な酸素分圧の低下があることを圧センサーを用いて証明した（図4）。さて、洞内酸素分圧の低下は何を意味するのであろうか。in vitroの嫌気培養系であるが、鼻粘膜から分離した線維芽細胞を用いて上清中のメディエーターを測定すると、血管内皮細胞増殖因子（vascular endothelial cell growth factor; VEGF）の産生亢進が認められたという。VEGFは血管新生作用や血管透過性亢進作用を強力に誘導する物質であり、この物質が洞粘膜の浮腫を起こし炎症を惹起する可能性はあると考えられる。

#### 感染

アレルギー性鼻副鼻腔炎症例の鼻汁細胞を調べてみると、好酸球が80%、好中球が40%の出現率であった（表2）。これを年齢別で比較すると、好酸球の出現率は年齢別で差はないが、好中球は10歳未満の症例において出現率が高く、さらに好中球が出現している症例の方が副鼻腔陰影出現率が高いことが分かった（図5）。このことは、臨床的には小児アレルギー性鼻炎症例では、アレルギーもベースにもち、かつ感染による副鼻腔炎の頻度が高率にみられることを示唆している。

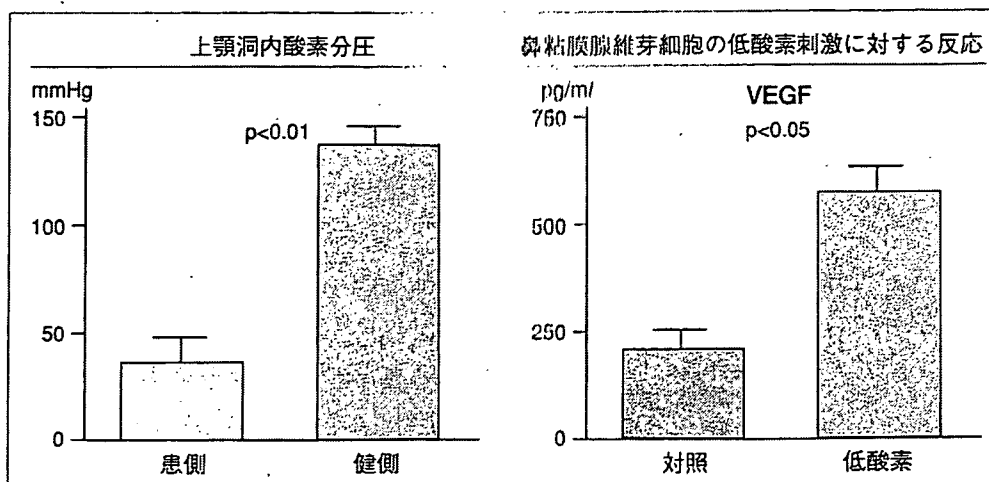


表2 鼻汁中の細胞陽性率

	陽性	陰性
好中球	19 (40%)	29
好酸球	38 (79%)	10

n = 48

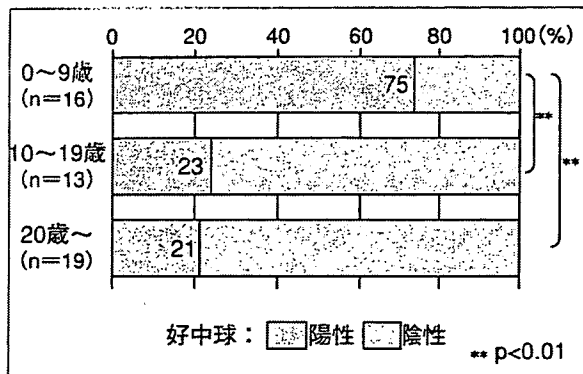


図5 年齢別鼻汁中好中球陽性率

さて、上顎洞貯留液からはグラム陰性桿菌に含まれるエンドトキシンやそのリガンドであるsCD14が高頻度に検出されることが報告されている。その濃度は化膿性鼻副鼻腔炎と差を認めないという。また、*in vitro*では鼻粘膜分離培養線維芽細胞にエンドトキシンを加えると、IL-8、RANTESなど好中球や好酸球の走化因子が産生されることが分かっている。すなわち、感染を契機としたアレルギー性鼻副鼻腔炎では好中球と好酸球の両者が出現し、その病態は複雑になる。

## 診断

● 症状：くしゃみ、鼻汁、鼻閉、後鼻漏、頭痛などの鼻副鼻腔炎症状を認める。

● 所見：ダニなどの通年性の典型例では、下鼻甲介粘膜の蒼白、腫脹が認められる。中鼻道視診により、中鼻甲介の肥厚や浮腫、中鼻道の閉塞や中鼻道に漿液性あるいは膿粘性の鼻汁の貯留、鼻茸が認められれば副鼻腔炎の可能性が高い。ただし中甲介、中鼻道に所見を認めない場合もある。

● 検査：副鼻腔X線検査にて上顎洞に肥厚性、ポリープ様陰影を認める。必要に応じて

副鼻腔CT検査を施行する。

鼻汁好酸球検査（ハンセル染色）にて好酸球の証明。

● 抗原の検査：皮膚テスト（皮内、スクッチ、プリック）陽性。血清IgE抗体検査陽性。鼻誘発テスト陽性。

（アレルギーの診断は鼻汁好酸球、皮膚テストあるいは血清IgE抗体検査、鼻誘発テストのいずれか2つが陽性であれば可）

上咽頭あるいは中鼻道からの菌検査で陰あるいは常在菌のみ。

## 鑑別疾患

### 化膿性副鼻腔炎

アレルギー検査は陰性。鼻汁検査で好中球多数。中鼻道に膿粘性鼻汁貯留。膿性後鼻漏。副鼻腔X線検査にて典型例はびまん性陰を示す。特に小児ではアレルギー性鼻炎に膿性鼻副鼻腔炎を合併している場合があるので注意が必要である。

### 好酸球性副鼻腔炎

春名らが提唱する副鼻腔炎である。嗅覚障害、耳閉感、難聴などを訴えることがある。典型例では乳白色のにかわ状の鼻汁。鼻汁には多数の好酸球を認める。ときに中耳炎併発することがありにかわ状の耳漏が特徴である（図6）。耳漏中に好酸球を多数認める。重症化すると感音性難聴を併発することがある。アスピリン喘息など成人型発症の管支喘息を合併することが多い。

### アレルギー性真菌性副鼻腔炎

慢性副鼻腔炎症例の4~7%がアレルギー性真菌性副鼻腔炎と報告されている。Bentの診断基準では、①CTにて慢性副鼻腔炎所見、②鼻茸を有する、③アレルギー性ムンを有する、④組織学的あるいは培養検査で真菌の証明、⑤既往歴あるいは皮膚テスト血清IgE抗体検査によるI型アレルギーの断を満たすものをいう。