Pathogenesis of Nasal Polyps

Tae Young Jang M.D.

ABSTRACT
While polyposis in the nose and paranasal sinuses continues to be a major clinical problem, the pathogenesis of nasal polyps remains controversial. Many etiologic theories, including those pointing to allergy, have been suggested. Most of the recent studies on nasal polyps focus on two key areas: the molecular and cellular network of the inflammatory process and the mechanisms behind polyp growth. Inflammatory changes in nasal mucosa can increase the effector capabilities of structural cell-derived cytokines, and represent a major amplification pathway of the inflammatory response in nasal polyps. The resultant edema can lead to the growth of nasal polyps. The role of allergy in the pathogenesis of nasal polyps remains unclear, but allergy may be one mechanism driving the chain of events leading to inflammation.

KEY WORDS Nasal polyps · Pathogenesis · Allergic rhinitis · Cytokines.

INTRODUCTION
Nasal polyposis is a common disease that severely affects daily life in most sufferers. Nasal polyps were first described more than 3000 years ago and comprise the most common group of mass lesions encountered in the nose. Despite this long history and the frequency of occurrence, a great many questions still exist with regard to its incidence, treatment, and pathogenesis. Numerous hypothesis have been formulated to explain the cause and mechanism of nasal polyps, but it would be fair to say that presently no one theory adequately explains the formation of all nasal polyps.1) Many of the etiologic theories discuss allergy,2) infection,3) dysfunction of the autonomic nervous system of the nose,4) abnormalities of the mucopolysaccharide metabolism,5) vasomotor imbalance,6) enzyme abnormality,7) the sensitivity to aspirin or imbalance of arachidonate metabolite production,8) mechanical obstruction,9) the role of histamines10) and proto-oncogenes.11) Allergy has been most frequently mentioned in the literature. But recent advances in the basic sciences, particularly in immunology and molecular biology, and recent works on the pathogenesis of nasal polyps provide a better understanding of two key points: the molecular and cellular network of the inflammatory process12) and the growth mechanism growth of polyps13)-21).

The role of allergy in the pathogenesis of nasal polyps
The major features pointing to allergy as a cause of nasal polyps include frequent clinical complaints of rhinorrhea, sneezing, and nasal itching; an elevated histamine level and the presence of IgE in extracellular polyp fluid; degranulated mast cells in the polyps; marked tissue eosinophilia; and an association of polyps with atopic diseases such as asthma and aspirin-sensitivity. These findings have led some authors to postulate that IgE-mediated reactions may be of primary importance.22) Kaliner23) has demonstrated that preformed mediators are released from polyps after IgE sensitization and Bumsted,24) after assaying polyp tissue, noted extremely high levels of histamine. Whiteside25) has shown IgE to be present on the surface of lymphocytes from some nasal polyps and the presence correlated with serum total IgE levels; those patients whose history and skin tests labeled them non-atopic did not demonstrate IgE-bearing cells in their polyp tissue. Other studies have documented elevated IgE levels in nasal polyp fluid.
mainly in atopic patients. However, recent studies have cast great doubt on the importance of allergy or IgE-mediated hypersensitivity in the etiologic development of nasal polyps. Studies of serum from patients with "atopic" diseases and/or polyps are often inconsistent in revealing that IgE mechanisms do indeed occur. Epidemiologic data strongly suggest that nasal polyposis occurs more commonly in nonatopic patients than in atopic patients. Caplin found that only 0.5% of a subpopulation of patients with nasal polyps had nasal polyps. Settipane found that nasal polyps are statistically more common in nonallergic asthma versus allergic asthma (13% vs 5%). Small, after an assessment of 29 patients with nasal polyps, found that elevated serum total IgE levels in 13 patients did not correlate with skin test and that increased serum immune complexes detected in 11 patients did not correlate with a depressed complement. These findings suggest a role of allergic mechanisms in just a minority of patients with polyps. On the basis of positive skin prick test and serum RAST results, Sin has shown that 45.2% of all patients with nasal polyposis were defined as allergic and that both total IgE and IgG4 were detected at increased levels only in the positive skin prick test group. These findings suggest that an IgE-mediated mechanism may be present in a subpopulation of patients with nasal polyposis.

Drake-Lee, utilizing careful history, skin and RAST test found no evidence of an increased incidence of allergic disorders in 200 consecutive patients admitted for polypectomy, and insisted that, although there did seem to be a genuinely atopic group, the incidence was no more than would be expected by chance alone. In another study comparing children who had both cystic fibrosis and polyps with children who had cystic fibrosis only, there was no evidence in history, skin test, or IgE levels that the patients with polyps were more allergic and Drake-Lee points out that there are many causes of eosinophilia, elevated histamine levels, and mast cell degranulation other than those that are IgE-mediated. Furthermore, he found no difference in polyps histamine levels between patients with allergic rhinitis and positive skin tests and patients without allergic rhinitis and positive skin tests, and found positive RAST to inhalant allergens in polyp fluid and positive in vitro challenge of polyp tissue with allergen extracts and anti-IgE in only a minority of patients. Davidsson’s study of a series of 95 consecutive patients who have had a polypectomy also supports the argument that allergy is not the only cause of nasal polyps and that the accumulation of eosinophilic granulocytes observed in most polyps is often not related to allergy. Lee investigated the expression of various cytokine messenger RNAs in nasal polyps and found no differences in the mean density ratios of each cytokine band on a Southern blot between polyp tissues with allergy and those without allergy. Min also found the same result.

In a morphological study on the distribution of inflammatory cells of nasal polyps, Ruhno states that epithelial mast cells in nasal polyps are equally elevated in nonallergic and allergic patients. Pawliczak found that regardless of whether or not atopy was present, eosinophils were the predominant cells in the polyps, and both eosinophils and mast cells were more abundant in the superficial layer than in the stromal layer of the mucosa. Pawliczak’s study also reports that eosinophils and mast cells are abundant in nasal polyps from both atopic and nonatopic patients and that mast cells seem to be more superficially distributed in atopic patients than in nonatopic patients. But in another study on the distribution of mast cells in nasal polyps, mast cells have been shown to be more frequent in the submucosa than in the epithelium of nasal polyps, indicating that an IgE-mediated degranulation of mast cells is probably not a causal factor. In summary, clinical features, skin test, IgE, histamine, and RAST level results of challenge to the polyp tissue suggest that allergic reactions occur frequently in patients with nasal polyps.

Allergy, however, may be one cause of an irritant reaction like bacterial infection in the development of an inflammatory change in the mucosa. The further infiltration of inflammatory cells, the release of cytokines, ulceration and prolapse of the submucosa, and edema of the mucosa represent an initiation of the major amplification pathway (Slavin named it the final common pathway for the formation of nasal polyps) of the inflammatory response in the formation and growth of nasal polyps. This reaction may induce enough swelling of the nasal mucosa to pinch off eventually with the help of gravity. Concomitant mucosal injury, interference with sinus drainage, and the hindrance of ciliary action would then create a static environment susceptible to bacterial invasion, resulting in sinusitis. In turn, sinusitis would cause venous stasis and mucosal edema, leading to further enlargement of the polyps.
The molecular and cellular network of the inflammatory process in the pathogenesis of nasal polyps

The nasal respiratory epithelium should be regarded not only as acting as a barrier but also as playing an active role in the pathophysiological processes leading to nasal polyposis. Morphological changes, such as secretory hyperplasia and squamous metaplasia, are also frequently observed in the epithelial lining of nasal polyps. Animal models with experimentally induced polyps exhibited a number of cellular events as being involved in the growth of the polyps epithelial desquamation induced by inflammatory reaction, epithelial proliferation, and differentiation with formation of microcavities and occasionally glands and progressive development of mucosal polyps related to circulatory disturbance and inflammatory substances. Coste has found that inflammatory changes can stimulate certain suprabasal cells, which would normally be undergoing maturation and differentiation, to undergo further proliferation. These findings suggest modifications of normal epithelial differentiation and proliferation, and increased epithelial proliferation could play an important role in the pathogenesis of nasal polyps, as well as in the inflammatory reactions of the lamina propria.

Inflammation with infiltration of inflammatory cells could at least be partly involved in the increased epithelial cell proliferation in nasal polyps. Studies on cell proliferation using flow cytometry and immunohistochemistry have shown that cell proliferation increases in nasal polyps, especially in the epithelium. Inflammatory cells, such as eosinophils, which are particularly numerous in nasal polyps, are able to induce epithelial damage, which can be repaired by increased epithelial cell proliferation. Harlin has also found that eosinophils and their mediators can damage the respiratory epithelium of paranasal sinus mucosa. The proliferation of epithelial cells was clearly correlated with the intensity of local inflammation in the duodenitis.

In the course of this disease, as is the case with nasal polyposis, inflammatory reactions may damage as well as stimulate epithelial cell proliferation. Inflammatory cells are also able to secrete several growth factors known to induce the proliferation of airway epithelial cells. Cells other than inflammatory cells (e.g. fibroblast and epithelial cells themselves) are able to produce growth factors and could indeed stimulate epithelial cell proliferation.

Stoop has observed the distribution of cells in polyps with normal tissue. Significantly more CD8 (suppressor/cytotoxic) than CD4 (helper/inducer) cells were found in the polyps and the macroscopically unaffected mucosa of the middle turbinates of the patients, supporting the suppressive and down regulating effect on the chronic inflammatory response of CD8 cells. In combination with the relatively low number of CD4 cells, this could perhaps indirectly result in a less sufficient humoral immune response but is certainly evidence of an altered T cell-mediated immune defense. The moderate to high infiltration of eosinophils is indicative of a chronic inflammation and is in accordance with the high prevalence of nasal polyps in patients with eosinophilic nonallergic rhinitis. The data presented suggest an association between the pathogenesis of nasal polyps and chronic inflammation and T cell-dependent disturbances in specific sites of the nasal mucosa. Recent studies support the theory that cytokines play a key role in the pathogenesis of nasal polyps. Allen has found that interleukin (IL)-3, IL-5, and granulocyte-macrophage colony-stimulation factor may dominate the nasal polyp microenvironment and directly contribute to the eosinophil chemotaxis, proliferation, and increased life span. This may enhance eosinophil-mediated tissue derangement, eosinophil recruitment/activation and likely play a key role in nasal polyp formation. Based on findings from experimental models, it seems reasonable to speculate that the formation and growth of nasal polyps requires extracellular matrix accumulation. Fibroblastic cells, which are the cellular source of extracellular matrix proteins, could therefore be involved in the nasal polyp growth process. Although their origin in smooth muscle cells has been suggested, myofibroblasts represent an activated cell phenotype of fibroblast with tissue contractile properties and a high capacity for extracellular matrix protein secretion. Various cytokines, such as granulocytic-macrophage-colony stimulating factor, platelet-derived growth factor, and transforming growth factor beta (TGF-β), induce myofibroblast development. Ohno detected TGF-β in nasal polyps but not in nasal mucosa. Eosinophils and macrophages, which have been reported to express TGF-β in nasal polyps, are likely to be the main source of TGF-β in nasal polyps. Wang states that TGF-β is
locally produced by inflammatory cells such as eosinophils and macrophages infiltrating nasal polyps, may induce myofibroblast proliferation and differentiation, and may also participate in the growth of nasal polyps by attracting fibroblasts and by enhancing extracellular matrix accumulation. Rudack51) found that in bilateral nasal polyposis, and not in antrochoanal polyps, the eosinophil-related cytokine IL-5 was strongly up-regulated, and suggests that IL-5 may represent the most important cytokine responsible for tissue eosinophilia in nasal polyps. Bachert52) also pointed to IL-5 as a key protein in the pathomechanism of tissue eosinophilia in nasal polyposis. Eisma53) found the presence of TGF- in the pathomechanism of tissue eosinophilia in nasal polyposis. Coste16) found evidence suggesting that increased local production of epithelial cell proliferation in nasal polyps and activated macrophages could be involved in the up-regulation of epithelial cell proliferation in nasal polyps and that this could also be involved in the pathogenesis of nasal polyps via its connective tissue remodeling actions. Basic fibroblast growth factor (bFGF) is a polypeptide that is mitogenic for a wide variety of cell types and mast cells are one source of this growth factor. It may also contribute to the endothelial and epithelial proliferation in nasal polyp tissues.

The growth mechanism of polyps

Many investigators have tried to induce polyps from maxillary sinus or middle ear mucosa instead of deducing from the histopathological view of the fully developed polyp. The role of edema versus epithelial damage in the initial stage of polyp pathogenesis is debated.

In recent years, investigations have focused primarily on mucosal edema and attributed its cause to such different factors as mast cell degranulation, vascular congestion, and altered ion transport mechanisms of the epithelium. However, Tos56) has put forward a pathogenetic theory, in which the first stage is epithelial rupture and the formation of granulation after infiltration and edema in the nasal mucosa where polyps are formed. While some investigators claim that the polyp surface epithelium does not rupture, others state that such ruptures occur frequently and may be attributed to the injurious effects of eosinophil-derived major basic protein50) or cytotoxic agents from granulocytes. Norlander9) and Lasen17) insist that mucosal edema per se is not necessary for the initiation of polyp formation and that epithelial damage is important for the initiation of polyp formation.

The histological features of inflamed mucosa suggest several possible causes of the initial epithelial rupture. The exudation of liquid, and thus the presence of large intraepithelial liquid vacuoles and the subsequent accumulation of liquid, distend and concurrently weaken the epithelial lining. The passage of luminally migrating inflammatory cells through the epithelium requires temporary breakdown of the lateral contact complex (zonula occludens, zonula adherens, macula adherens) between adjacent epithelial cells. Furthermore, noxious and cytotoxic agents such as the lysosomal enzyme of the granulocyte are released, so subsequent damage to and further weakening of the epithelium is inevitable. It is believed that the interaction of one or more of the factors mentioned above, together with generalized mucosal edema, cause the initial epithelial rupture, and thus form the basis of subsequent polyp formation.

Norlander9) has observed polyp formation in New Zealand white rabbits through different modes of manipulation intended to induce inflammation of the maxillary sinus. The manipulation process includes a combination of bacterial infection and mechanical trauma, and the deposition of agarose or irritative chemicals into the sinus cavity. He observed the polyp formation through a light and transmission electron microscope and found that it appears to involve epithelial disruption and the migration of immature branching epithelium. While part of the migrating epithelium eventually covers the mucosal defect, other branches spread into the underlying connective tissue, where intraepithelial microcavities with a differentiated, ciliated lining are formed within the deeper layer of the invading epithelium. These cavities gradually fuse, allowing the wall of the forming polyp to separate from the sinus mucosal surface and a stalked...
polyp is thereby eventually formed. Norlander explains the histologic differences between epithelial-rich and granulation-rich polyps as two ends of a continuum that contains a variety of intermediate forms led by the varying degree of bacterial infection or mechanical trauma.

In studying mucosal infection, Lasen \(^\text{17}\) divided the pathogenic theory of polyp into five stages, the first stage of which involves an epithelial defect or rupture with prolapse of fibrous tissue through the epithelial defect. This first stage of epithelial defect has not been proven histologically in the nose due to lack of suitable material at this stage. However, indirect support for the epithelial rupture theory in polyp formation has been reported in the literature. In studies dealing with experimental acute maxillary sinusitis in rabbits, epithelial defects in the mucosa and polyps have been observed locally. \(^\text{59,60}\) In addition, large epithelial defects in humans with chronic sinusitis have been looked at. \(^\text{51}\) In instances of short-term experimental tubal occlusion in rats, Lasen \(^\text{62}\) has found small polyp-like protrusions in the middle ear mucosa with epithelial degeneration and epithelial rupture. The second stage is the epithelialization of the prolapsed tissue by which a small polyp is established. The third stage is gland formation deriving from the polyp epithelium. This re-epithelialization of protruded tissue by cell division at the edges of the surrounding epithelium develop into a polyporous mucosal prominence. Thomsen \(^\text{58}\) found that the presence of goblet cells within the epithelium of polyps in mucosal areas that normally lack goblet cells indicates that the polyp epithelium is newly formed. Tos has shown in his previous studies of nasal polyps from patients with cystic fibrosis or without cystic fibrosis that most of the glands did not originate from the nasal mucosa but were new formations from the polyp epithelium. \(^\text{63}\) The fourth stage is growth of the polyp, partly active as a consequence of edema and partly passive due to stretching caused by gravity and aerodynamic conditions. The fifth stage indicates a fully developed polyp. In another study, \(^\text{64}\) he found that the epithelium, the stroma, and goblet cell density are constantly affected by airflow and internal influences on the mucosa, such as allergies and new infections.

It is generally agreed that diffuse edema is present in the mucosa. However, in addition, other factors must interact, since the polyp formation is localized to a distinct place in the mucosa. \(^\text{17}\) Nasal polyps appear to arise by far most commonly from the lateral wall of the nose or from the anterior ethmoid sinus mucosa. It is in this area that the aerodynamics are different from those in the lower third of the nose. \(^\text{60}\) In the lateral wall of the nose there is an increased turbulence of air molecules and therefore a greater chance of irritative factors being deposited in this area and triggering inflammation. Also in this area is a significantly greater number of immunocompetent cells in the middle turbinate and polyps compared to in the inferior turbinate mucosa. Thus immunologic response and the host response are greater in the areas in which nasal polypocnosis occurs.

REFERENCES


