REVIEW

Relation Between Rhinosinusitis and Bronchiectasis

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The nose and lungs have both histological and functional similarities and differences. Sinonasal and bronchial involvement are associated in many diseases. Cystic fibrosis, primary ciliary dyskinesia, Young's syndrome, and α-1 antitrypsin deficiency are diseases in which bronchiectasis and rhinosinusitis are both present. This review considers the diseases in which bronchiectasis occurs along with sinonasal manifestations. We propose examining sinonasal disease from a new perspective by observing it in patients with bronchiectasis.

Key words: *Rhinitis. Sinusitis. Bronchiectasis.*

Relaciones entre rinosinusitis y bronquiectasias

La nariz y el bronquio presentan similitudes y diferencias tanto histológicas como funcionales. Son muchas las enfermedades en que se asocian la afección nasosinusal y la bronquial. La fibrosis quística, la discinesia ciliar primaria, el síndrome de Young y el déficit de alfa-1-antitripsina son enfermedades en las que se asocian bronquiectasias y rinosinusitis. En este artículo se realiza una revisión de las bronquiectasias y de las enfermedades que las asocian junto a afección nasosinusal. El propósito es dar un nuevo enfoque de la patología nasosinusal observada en los pacientes afectados de bronquiectasias.

Palabras clave: *Rinitis. Sinusitis. Bronquiectasias.*

Introduction

Diseases that until recently were regarded as exclusively pulmonary or bronchial are increasingly being shown to occur in association with nasal and paranasal disease. The concept of rhinobronchitis has introduced the idea that the upper and lower airways are in fact a single airway and that diseases affect the whole respiratory system.[1] Many epidemiological studies have examined and confirmed this association, giving rise to the concept of "one airway, one disease," (Figure). The clearest example of this association is with rhinitis and asthma[2]; most asthmatics present both disorders and the treatment of rhinitis can be beneficial for asthma.[3]

The upper and lower respiratory airways have the common function of conditioning and channeling external air into the lungs. Within this shared function there are specific functions performed by different sections: humidifying, heating, filtering, phonation, and gas interchange.[4]

Nasal and Bronchial Mucosa

The epithelium and lamina propria of the nasal and bronchial mucosa are similar. A major function of the nose is to filter out harmful substances, both infectious and noninfectious ones. The nose also conditions inspired air, heating and humidifying it. The function specific to the nose and that most distinguishes it from the lower airways is, without doubt, olfaction, involving the pituitary gland, and located in the roof of the nasal cavity.[5]

The squamous epithelium of the nasal valve is transformed in the rest of the nose into a ciliated pseudostratified columnar respiratory epithelium. In the nose this columnar epithelium is formed by ciliated, nonciliated, basal, and goblet cells, and it differs from the epithelium of the lower airway by the absence of serous cells, Clara cells, or brush cells.[6] The basement membrane is composed of type IV collagen, proteoglycans, laminin, and fibronectin. The lamina reticularis is found below the membrane and is evenly thicker in asthmatic patients.[7] Focal thickening of the membrane is observed in patients with bronchiectasis, tuberculosis, and chronic rhinosinusitis[8] but no changes in this part of the structure have been observed in patients with rhinitis.[9]

In the submucosa, there are glands, blood vessels, nerves, extravascular cells, and extracellular matrix. One of the major structural differences is found here: the bronchial submucosa has smooth muscle whereas the nasal submucosa does not.[6]

Glands and blood vessels predominate in the nose. Apart from arterial vessels, nasal vasculature is formed by capillary beds, arteriovenous shunt, sinusoids, and venous vessels. The veins that drain the sinusoids have

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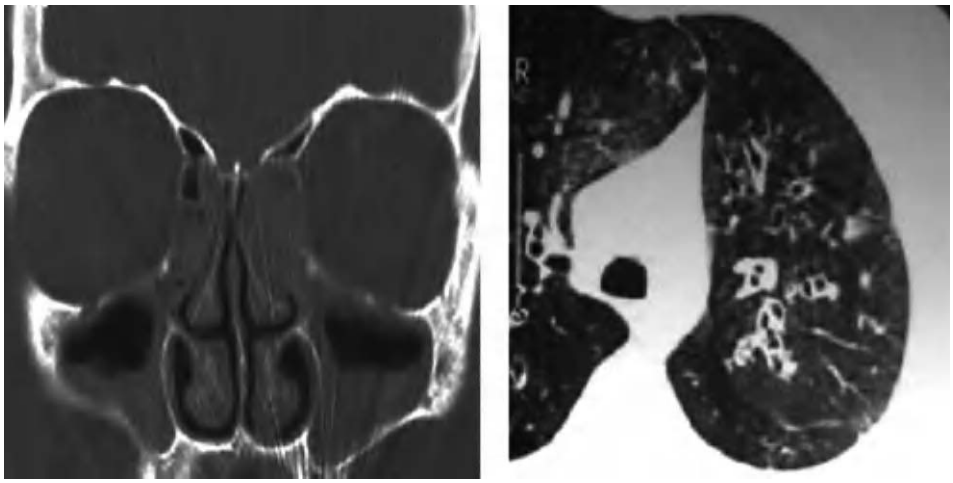

Figure. Chronic rhinosinusitis in the bilateral maxillary ethmoidal region (computed tomography scan of the sinus) beside a bilateral bronchiectasis (lung scan) in the same patient.

smooth muscle. When the veins contract, the sinusoids expand, increasing the size of the turbinates (erectile tissue), facilitating nasal flow. This does not occur in the bronchi where smooth muscle contraction increases flow resistance.

Mucociliary Transport

The mucociliary system is formed by many cilia, which protrude from the surface of the pseudostratified columnar epithelial cells. Each ciliated cell contains about 200 to 300 cilia which beat about 500 times per minute. Beat frequency decreases distally,[10] so frequency is lower in middle airways. Malfunction in this zone can lead to pooling of secretions and predisposition to local infections, possibly contributing to the development of bronchiectasis in this part of the respiratory airways.[11] Ultrastructural abnormalities in the cilia interfere with and prevent normal motility predisposing an individual to chronic and recurrent nose and sinus infections (chronic rhinosinusitis) and lung infections that lead to bronchiectasis.

Approximately 70% to 80% of asthma patients present rhinitis and recent studies have shown rhinitis to be a predisposing factor of asthma.[12] This has led to the performance of studies that aim to prevent asthma by providing early treatment of rhinitis.

Nasal polyposis is detected in 2% to 4% of the population but the prevalence rises to 7% among asthmatic patients. Polyposis is uncommon among patients with mild asthma but as the severity of the disorder increases, sinus infections and polyps become much more common to the extent that it is unusual to find a patient with asthma and intolerance to aspirin who does not have nasal polyposis.[13]

Relation between chronic obstructive pulmonary disease (COPD) and rhinitis has also been observed.[14] Biopsies of nasal mucosa in COPD patients have been found to contain similar inflammatory abnormalities to those of bronchial biopsies in the same patients.[15]

The association between respiratory symptoms and anterior and posterior rhinorrhea, adenoids, nasal congestion, and loss of smell reinforces the concept that upper and lower respiratory airways are related.[16]

Bronchiectasis

Bronchiectasis is the abnormal dilatation and destruction, permanent and irreversible, of one or more medium or small bronchi (from the fourth to the ninth generation), produced by the destruction of the muscular and elastic components of the bronchial wall. The prevalence in the general population is unknown and the natural history of the condition has not been studied from the beginning of the process and with posterior analysis of its progression.[17]

Laennec[18] first described bronchiectasis in 1819, noting that it was caused by the retention of bronchial secretions with secondary destruction of the wall and posterior weakening and dilatation of the same. This interpretation is still valid and bronchial inflammation is thought to play a central role. After contrast bronchography was introduced by Sicard in 1922, bronchiectasis could be seen with more precision.[19]

Etiology and Pathogenesis

Bronchiectasis is not a single disease but rather the result of the damage that can be caused by several different processes acting on the bronchial wall and which can interfere directly or indirectly with its defenses. Bronchiectasis can be diffuse or focal. Medium sized bronchi are usually dilated but often small bronchi can be enlarged or destroyed too. Sections of bronchial wall are destroyed and chronically inflamed, ciliated cells are damaged or destroyed, and mucus production is enhanced, the normal tone of the wall being lost. Increased mucus production encourages bacterial growth, obstructs the bronchi, and leads to pooling of infected secretions, with subsequent damage to the bronchial

wall.[20] The inflammation can spread to the alveoli and produce bronchopneumonia, formation of scar tissue, and loss of healthy lung tissue. Moreover, inflammation of the blood vessels in the bronchial wall can cause blood-stained sputum or frank hemoptysis. Examination by the pathologist reveals bronchial dilatation, mucosal hypertrophy sometimes with squamous metaplasia, lymphocytic infiltrates in the bronchial wall, and loss of cartilage, muscle, and elastic fibers—these last structures being replaced by scar tissue.[21]

Focal bronchiectasis is usually caused by stenosis of some bronchi through inflammatory processes, neoplasms, or foreign bodies.[22] Any circumstance that produces absorption collapse in the zone and fibrosis of the adjacent lung tissue contributes to the formation of bronchiectasis through compensatory dilatation of the bronchi.

Diffuse bronchiectasis has many possible causes (Table), in particular congenital diseases, which affect mucociliary function and include cystic fibrosis and dyskinesia (Kartagener's syndrome, Young's syndrome). It can also be associated with defects in defense mechanisms, which can lead to recurrent bronchial infections (common variable immunodeficiency, defective antibody formation). Some bronchiectases seem to have developed from infectious bronchiolitis in childhood (measles, syncytial respiratory virus). Bronchiectasis can also be associated with systemic diseases (rheumatoid arthritis, Sjögren syndrome) or inflammatory intestinal diseases (ulcerous colitis, Crohn's disease). In a few cases it is the consequence of aspiration of toxic substances, which damage the bronchi.

Bronchiectasis is classified into 3 types according to shape: cylindrical, varicose, and saccular (the last 2 tend to be clinically more severe).

Biopsy of the bronchial mucosa reveals infiltration by neutrophils and T lymphocytes,[21] as well as an increase in the elastase content of the sputum[23] and an increase in the interleukin-8 concentrations,[24] tumor necrosis factor-α,[25] and prostanoids.[26]

The most common complication of bronchiectasis is recurrent infection,[27] usually by *Haemophilus influenzae* (55%) and *Pseudomonas* species (26%).[28] Less common infectious agents are metastatic abscesses, mainly in the central nervous system (12%-16%), and amyloid type AA accumulations (6%). Other complications are pulmonary hypertension and chronic cor pulmonale. In saccular bronchiectasis, clubbing of the fingers is often found.

Clinical Manifestations

Although bronchiectasis can occur at any age, it usually starts in the first 20 years of a patient's life. The symptoms may not appear until much later or never, in some cases a radiologic diagnosis is made while the bronchiectasis is still asymptomatic. Common signs are cough with abundant expectoration (bronchorrhea), which is occasionally blood-stained. The quantity and type of sputum depends on the extent of the disease and the presence of an active infection. In some cases massive hemoptysis can occur. Pneumonia is relatively common and, in some patients, recurrent. Diffuse bronchiectasis can cause respiratory failure, pulmonary hypertension, and cor pulmonale.[29]

Diagnosis

Diagnosis is made on clinical and radiological evidence. A simple chest x-ray may show images such as tram lines, cysts, and bronchi filled with mucus (gloved fingers image) all of which are indicative of bronchiectasis although more often images are normal or show nonspecific signs such as an increase in bronchovascular markings. Nowadays, computed tomography (CT) of the chest allows certain diagnosis at the same time as it determines the location and extension of disease.[30] Since the introduction of CT, bronchography is no longer used in the diagnosis of bronchiectasis.

Lung function testing can reveal varying degrees of obstruction according to the extent of the disease, although mixed patterns are often seen, caused by loss of volume through the collapse of some lobes associated with the obstruction. Impaired gas exchange due to the existence of shunt zones can cause severe hypoxemia.[31]

Treatment

The main objective of treatment is to control infections and secretions and thus avoid airway obstruction and its complications. Effective respiratory physiotherapy is essential to expel the bronchial secretions. The reduction of some childhood viral

TABLE
Etiology of Bronchiectasis

Focal Bronchiectasis
Bronchial obstruction: foreign body aspiration, diseased lymph nodes, lung tumors, and mucus plug
Diffuse Bronchiectasis
Congenital: primary ciliary dyskinesia (Kartagener's syndrome), cystic fibrosis, α_1-antitrypsin deficiency, tracheobronchomegaly (Mounier-Kühn syndrome), cartilage deficiency (Williams-Campbell syndrome), Marfan syndrome, and pulmonary sequestration
Postinfectious: viral (paramyxovirus, adenovirus, influenza virus, human immunodeficiency virus); bacterial (*Haemophilus, Pseudomonas, Klebsiella, Staphylococcus, Bordetella, Mycobacterium [M tuberculosis], Mycoplasma [M pneumoniae]*); and fungal (*Aspergillus*)
Immune system disorders: primary (hypogammaglobulinemia, complementary deficiencies) and secondary (chronic lymphocytic leukemia, chemotherapy)
Toxic: inhalation of noxious fumes, aspiration of gastric content.
Systemic diseases: rheumatoid arthritis, systemic lupus erythematosus, Sjögren syndrome, recurrent polychondritis.
Others: inflammatory intestinal diseases (ulcerative colitis, Crohn's disease), yellow nail syndrome.

infections through vaccination has lowered the risk of bronchiectasis. Vaccination against pneumococcus and *Haemophilus* species and the annual influenza vaccination very likely reduce the number of serious infectious episodes.[32]

Diseases That Lead to Bronchiectasis and Associated Nasal Disease

Cystic Fibrosis

Cystic fibrosis is an autosomal recessive genetic disorder found above all among Caucasian peoples. One in 25 individuals carries the gene.[33,34] It is estimated to affect about 1 in every 3000 to 10 000 live births per year. The gene responsible for cystic fibrosis is found in a simple locus on the long arm of chromosome 7. The deletion of 3 pairs of bases or mutation delta F508 occurs in about 70% of all cystic fibrosis chromosomes. The defective protein—the cystic fibrosis transmembrane regulator—codified by this abnormal gene has a structure similar to that of a class of proteins known for being active in epithelial transport.[35] The defective protein contributes to the poor function of the chloride channels, causing an increase in mucus viscosity, which makes its elimination difficult and encourages the colonization of *Staphylococcus aureus* and mucoid *Pseudomonas aeruginosa.*

Many other mutations have been identified near the locus involved. Patients with cystic fibrosis present recurrent infections in the respiratory tract, pancreatic exocrine insufficiency, and infertility. In the early stages, chest x-rays show upper lobe involvement,[36] which spreads as the disease progresses. Lung function can be normal or display an obstructive or mixed pattern. Adult patients have often had symptoms of the disease for many years but, because they were moderate, they went unnoticed. Adults may present bronchiectasis, rhinosinusitis, pancreatic failure, acute pancreatitis, cholelithiasis, and infertility. Nasal obstruction is the most common symptom among cystic fibrosis patients, and more than 20% present nasal polyposis. There are several patterns of rhinosinusitis: nasal polyposis, chronic purulent nasal and sinus infection, and pyogenic mucus impaction of the maxillary antrum with bulging of the lateral nasal wall; this last type has been called maxillary pseudomucocele.[37] The sweat test is important in diagnosis,[38] as sodium or chloride concentrations are 60 mmol/L in cystic fibrosis patients whereas healthy individuals and cystic fibrosis gene carriers have concentrations of 30 mmol/L. Also important are genotyping and pulmonary and sinus CT. The treatment objectives are to reduce obstruction, control infections,[39] reduce inflammation, and improve nutritional status. Nasal treatment consists of lavage with saline solution, intranasal corticosteroid therapy, antibiotic therapy, and, when necessary, functional endoscopic surgery on the sinuses.

Primary Ciliary Dyskinesia

Primary ciliary dyskinesia (PCD) is a congenital disease which affects, totally or partially, the function of the ciliated cells.[40] It is an autosomal recessive disorder, which affects 1 in every 16 000 live births and presents clinically as rhinosinusitis, bronchiectasis, and less often, sterility among men. In the primary ciliary dyskinesia syndrome (dyskinesia refers to difficulty of movement) there is structural and functional impairment in the cilia microtubules, which are responsible for motility. This dysfunction prevents the cilia from clearing the mucus, causing purulent bronchial infections and bronchiectasis. All ciliated structures can be involved: epithelia of the respiratory airways, paranasal sinuses, the eustachian tube, and spermatozoids (asthenospermia).[41]

About 50% of patients present Kartagener's syndrome, characterized by the triad of bronchiectasis, rhinosinusitis, and situs inversus (dextrocardia).[42,43] Rhinitis with anterior rhinorrhea is found in all PCD patients, accompanied in some by nasal polyps and the reduction or complete loss of the sense of smell. A sinus CT scan often shows invasion of ethmoidal and maxillary sinuses, together with hypoplasia of the frontal sinus. Diagnosis is based on a battery of tests: saccharin time, nasal nitric oxide, and nasal biopsy in which ciliary beat and density is observed with an electronic microscope.[44] The mainstays of PCD treatment are respiratory physiotherapy with postural drainage and antibiotic therapy for exacerbations of respiratory infections. Endoscopic polypectomy or functional surgery of the sinuses is beneficial in patients with chronic rhinosinusitis which does not respond to treatment.

Diagnosis is established by the study of the ultrastructure of nasal mucosal samples, in which absence of the dynein arms or abnormal position of the microtubules can be seen. Recent studies have shown low concentrations of nasal nitric oxide in those patients.[45]

Young's Syndrome

Young's syndrome is characterized by the triad of bronchiectasis, chronic rhinosinusitis, and infertility. Patients present normal ciliary activity and highly viscous mucus. Nasal biopsy material does not show changes in ciliary structure under an electronic microscope.[46] The azoospermia causes infertility by obstructing the epididymis, although spermatogenesis is completely normal. Diagnosis is based on clinical signs (chronic sinopulmonary disease, azoospermia), and the exclusion of cystic fibrosis and immotile-cilia syndromes.[47]

α_1-*Antitrypsin Deficiency*

α_1-antitrypsin, a glycoprotein produced by liver cells, inhibits proteases (elastase), particularly those released by neutrophils while repairing and cleaning agents

outside the lung. The inhibition of proteases prevents the destruction of healthy tissue in the organism.[48] The codifying gene is located on chromosome 14. α_1-antitrypsin deficiency of the lung produces emphysema by progressively destroying the alveoli in individuals aged 30 to 50 years. Tobacco smoke contributes to lung destruction by increasing elastase activity, decreasing α_1-antitrypsin activity by oxidation, and stopping elastin synthesis, preventing lung repair. Cessation of smoking should consequently be high priority for patients diagnosed with α_1-antitrypsin deficiency.[49]

Emphysema produced by α_1-antitrypsin deficiency is panacinar, destroying the entire acinus, and is usually found in the bases. Lung compliance increases. Reduction of α_1-antitrypsin concentrations produces an imbalance between this protein, an antiprotease, and elastase, a protease. α_1-antitrypsin deficiency enables elastase to progressively destroy the elastin in the alveolar walls.[50] Normal rates of α_1-antitrypsin protein in blood are considered to be between 150 and 350 mg/dL or 20 and 53 μM and at concentrations of less than 80 mg/dL or 11 μM there is risk of developing one of the deficiency diseases.[51] The second most affected organ is the liver, especially in newborn babies and children. Patients present a history of α_1-antitrypsin deficiency or lung disease including emphysema, chronic bronchitis, bronchiectasis, asthma resistant to treatment, and recurrent pneumonia. Quantitative α_1-antitrypsin measurement is recommended in patients with precocious emphysema, a family history of the condition, dyspnea or cough in several members or generations of the same family, adults with bronchiectasis of unknown etiology, obstructive pulmonary disease, liver disease of unknown origin, asthma which does not respond to treatment, and panniculitis of unknown origin.[52] Allergic rhinitis and recurrent rhinosinusitis are also common even in the absence of obstructive pulmonary disease.[53]

Conclusions

Consistent with the concept of "one airway, one disease," bronchiectasis patients often present sinonasal involvement. The prevalence of the association is not known as systematic studies have not been carried out. It is not known, for example, whether the microbes which colonize the lower airways are responsible for the nasal process or whether the characteristics of the lower airway inflammatory process are similar to nasal and sinus processes. Given that the nose is more accessible for examinations (endoscopy, biopsy, nasal secretion collection) compared to the lower airways, which must be examined by fiberoptic bronchoscopy, monitoring the nose might offer an easier and less invasive way to follow lung disease progression. The treatment of allergic rhinitis and nasal polyposis has been shown to improve asthma progression, but it is not known if there is a similar relation between sinusitis and bronchiectasis. Demonstrating the similarity of infectious and inflammatory processes in the upper and lower airways of patients with bronchiectasis would allow studies to be performed to clarify the mechanisms responsible for the origin of this disease.

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