

Atrophic rhinosinusitis: progress toward explanation of an unsolved medical mystery

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Purpose of review

Atrophic rhinosinusitis is a chronic condition associated with considerable morbidity and decreased quality of life. This review describes progress in the characterization of primary and secondary atrophic rhinosinusitis and the development of diagnostic criteria for both syndromes.

Recent findings

Primary atrophic rhinitis usually develops as a consequence of an acute febrile illness in members of lower socioeconomic groups in developing areas of the world. The clinical setting and presence of culturable *Klebsiella ozenae* in the purulent, foul-smelling, nasal discharge of these patients forms the basis for diagnosis. An animal model for the disease exists in swine in which case an effective vaccine has been developed.

Secondary atrophic rhinosinusitis is a condition that follows destruction of the nasal mucosa by any of a number of inflammatory processes including inflammatory diseases nasal/sinus surgery, and antiangiogenic therapy. Diagnostic criteria include patient reported recurrent epistaxis or episodic anosmia; or physician documented nasal purulence, nasal crusting, chronic inflammatory disease involving the upper airway (e.g. sarcoidosis, Wegener's granulomatosis, etc.) or two or more sinus surgeries. Patients with two more of these have secondary atrophic rhinitis with a sensitivity of 0.95 and a specificity of 0.77.

Summary

Atrophic rhinosinusitis results from destruction of the normal respiratory epithelium and transition to a nonciliated squamous epithelium, loss of mucociliary clearance, accumulation of stagnant mucous. That milieu facilitates acute and chronic infection (wet phase), and eventual sclerosis with epistaxis and chronic bloody crusts (dry phase).

Keywords

atrophic rhinitis, *Klebsiella ozenae*, rhinosinusitis

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Introduction

Atrophic rhinitis has been recognized since the time of the Pharaohs when Egyptian physicians recommended treatment for it with date wine and breast milk in the Edwin papyrus (1700 BC) [1]. It was characterized by Fraenkel in the modern era as a triad of symptoms consisting of a foul nasal odor, mucous membrane atrophy, and crust formation [2]. The terms atrophic rhinitis, rhinitis sicca, and ozena were used interchangeably in the scientific literature, until Ruskin differentiated the primary from secondary forms [3].

Primary atrophic rhinosinusitis

The 'primary' form occurs primarily in young adults living in developing countries [4]. The disease is most

frequent in Southern Saudi Arabia, China, Africa, India, the Mediterranean area and Philippines [5]. It must be considered in the differential diagnosis of immigrants from those areas. Progressive nasal mucosal atrophy with resorption of underlying cartilage results in widened nasal passages, paradoxical nasal congestion, and intractable nasal secretions early on and dry bloody crusts later in the course of the disease [6]. The distinctive feature is a fetid odor, ozena (Greek for 'the stench'), that is readily detectable by others. The odor results from infection of the nasal passages with *Klebsiella ozenae*, the organism most frequently cultured from the nasal discharge [7]. Those affected are frequently ostracized from their communities.

The condition has been reported among multiple individuals in the same family and in swine (see below)

suggesting a transmittable, infectious cause. Some feel that the infection with *K. ozenae* is the proximate cause of atrophic rhinosinusitis and the granulomatous nasal disease, rhinoscleroma, is caused by a related organism, *K. rhinoscleromatis* [8]. However, other gram-negative bacteria, primarily *Pseudomonas aeruginosa* and *Escherichia coli*, have also been associated. Bacterial lipopolysaccharides from all of the organisms have the potential to induce ciliostasis and generate biofilms associated with resistance to host defenses and antibiotics. Fungal elements, especially those of aspergillous species, are also common in nasal purulence and crusts [9].

Secondary atrophic rhinosinusitis

The more common form of atrophic rhinitis is clinically distinct from the primary form, and is seen in the US and other developed countries [10^{••}]. Little is known about this 'secondary form' and it remains incompletely characterized. It has occurred in association with chronic granulomatous diseases of the nose, including tuberculosis, syphilis, leprosy, sarcoidosis, rhinoscleroma, and Wegener's granulomatosis. The onset after treatment with antiangiogenic drugs underlines the role of the microvasculature in the pathogenesis [11[•]]. It has also been associated with extensive sinus surgery, often involving radical turbinectomies (empty nose syndrome), nasal or sinus injuries and radiation therapy to the area [12]. Symptoms associated with secondary atrophic rhinosinusitis include chronic nasal obstruction, purulent postnasal drip, nasal crusting, epistaxis, and episodic anosmia [13]. In our experience, it is uncommonly associated with resorption of the underlying turbinates or a fetid odor.

Recent case series of primary and secondary atrophic rhinosinusitis: Mayo clinic series

The largest case series of patients with atrophic rhinitis included 242 patients seen between 1982 and 1999 at a large referral center in the US [13]. The countries of origin of the patients were not provided. The authors used a consensus diagnosis of atrophic rhinosinusitis as their sole inclusion criterion for patients. Those with no history of nasal trauma, sinonasal surgery, granulomatous disease, or radiation to the sinonasal area were assigned to the primary atrophic rhinitis group and all others formed the secondary atrophic rhinitis group. The majority had secondary atrophic rhinosinusitis ($n = 197$). Several features were thought to be common to both forms including nasal crusting, enlarged nasal cavities, resorption of the turbinates, mucosal atrophy, and paradoxical nasal congestion (given below).

Computed tomography and histopathologic findings in 242 patients with atrophic rhinosinusitis (adapted from [10^{••},13]):

Key points

- The presence of secondary atrophic rhinosinusitis should be considered in patients with chronic, non-allergic rhinosinusitis who have had previous nasal injury or inflammation.
- Primary atrophic rhinitis is associated with a foul-smelling nasal discharge which is culture-positive for *Klebsiella ozenae*.
- An excellent animal model of primary atrophic rhinosinusitis has been characterized in swine.
- A nasal biopsy should be considered in patients with possible secondary atrophic rhinosinusitis.
- Nasal lavage is a useful approach to management of atrophic rhinosinusitis.

- (1) Computed tomography
- (2) Atrophy of serous and mucinous glands
- (3) Loss of cilia and goblet cells
- (4) Inflammatory cell infiltrate (not characterized)
- (5) Endarteritis
- (6) Histopathological findings
- (7) Mucosal thickening of the paranasal sinuses
- (8) Loss of definition of the osteomeatal complex secondary to destruction of the ethmoid bulla and uncinate process
- (9) Hypoplasia of the maxillary sinus
- (10) Enlargement of the nasal cavities with destruction of the lateral nasal wall
- (11) Bony destruction of the inferior and middle turbinates

The authors concluded that 'The only distinction in the two diseases is cause'. 'Spontaneous onset, slow progression and unspecified cause' were thought to be distinguishing characteristics of primary atrophic rhinitis. The authors noted that primary atrophic rhinosinusitis was associated with 'progressive loss of the nasal mucosa and underlying bone of the sinuses', whereas secondary 'atrophic rhinitis rarely involves the submucosal tissues until late in the disease'.

They also noted that certain histopathologic features were common to both forms (listed above). Vascular changes were thought to lead to epithelial damage and crusts. They found that findings on sinus computed tomography were similar in both groups and were those previously described [14]. Nasal cultures were positive for *K. ozenae* in all 45 patients with primary atrophic rhinitis and 3 patients with the secondary form. Five patients with primary atrophic rhinitis had a sibling affected with the disease.

In the secondary atrophic rhinosinusitis group, 176 of 197 patients had previous nasal surgery and 157 had turbinectomy in that process. The reasons for those surgeries

were not given but could be helpful in better understanding the pathogenesis of the disease. The remainder of the 197 patients had sinus surgery without turbinectomy for neoplasia, nasal obstruction or granulomatous disease. Finally, they concluded that rhinitis sicca, one of the terms previously used to describe atrophic rhinitis, was a 'distinct disorder of uncertain cause characterized by drying of the nose and mucosal hypertrophy rather than atrophy of the nasal mucosa'.

Our series

Our group sought to determine specific criteria that would facilitate the diagnosis of secondary atrophic rhinosinusitis and future clinical treatment trials of the condition [10^{••}]. Twenty-two patients from our clinic with a consensus diagnosis of secondary atrophic rhinosinusitis were compared to a control group of 22 individuals with garden variety chronic allergic or vasomotor rhinosinusitis. All patients in both groups were residents of the contiguous US. We found that certain combinations of criteria clearly distinguished patients with secondary atrophic rhinosinusitis from control patients. Each of the originally proposed criteria (given below), other than nasal obstruction, occurred more frequently in patients with secondary atrophic rhinosinusitis than controls. Patients with any combination of two or more proposed criteria had an odds ratio (OR) of 8.9 and were over 80 times more likely to have atrophic rhinosinusitis than an individual with none of these criteria. Excluding nasal obstruction, two or more criteria were associated with a sensitivity of 0.95 and a specificity of 0.77 for the condition.

Criteria for the diagnosis of secondary atrophic rhinosinusitis evaluated in our study (from [10^{••}]):

- (1) Recurrent epistaxis
- (2) Episodic anosmia
- (3) Nasal purulence
- (4) Nasal crusting
- (5) Chronic inflammatory disease of the upper airway for 6 months
- (6) Two or more sinus surgeries
- (7) Nasal obstruction (not included in proposed criteria after our study)

There was a spectrum of nasal findings ranging from mucopurulent, the 'wet form' (Fig. 1) of the disease, to a drier, crusted form (Fig. 2) [10^{••}]. We were surprised to hear from our patients with the 'dry form' how frequently they used tweezers to remove bloody crusts from their nose to relieve nasal obstruction.

Sinus computed tomography findings established that the majority of patients had both rhinitis and sinusitis, supporting our contention that the condition should be best

Figure 1 Rhinoscopic view in atrophic rhinosinusitis through a nasal septum perforation reveals bilateral middle turbinectomies, copious yellow mucopurulent secretion, edema, and minimal crusting



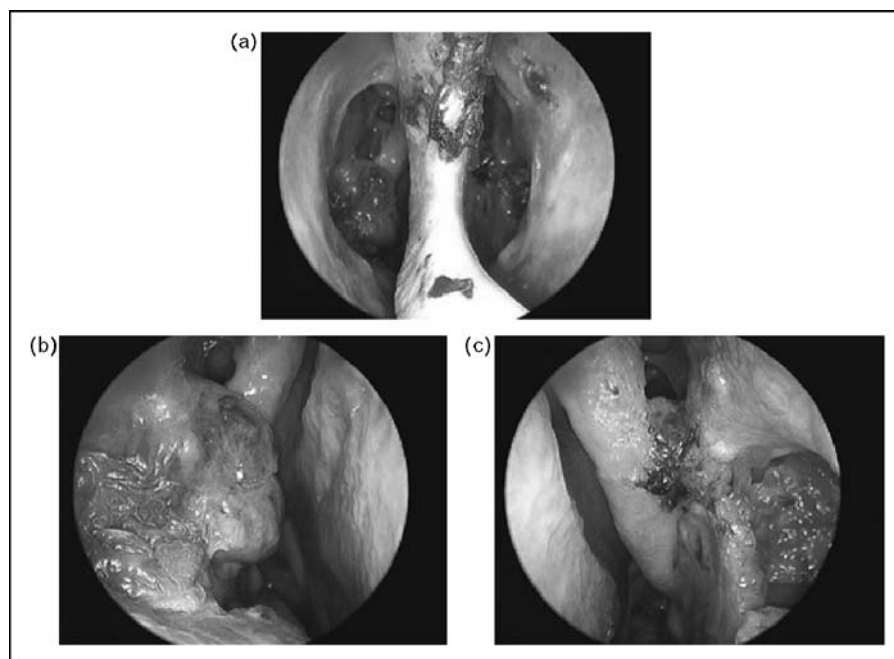
Reproduced with permission from [10^{••}].

termed atrophic rhinosinusitis. Almost half of the patients with atrophic rhinosinusitis in our study were atopic and the majority had multiple sinus surgeries, of which two-thirds included a partial or radical turbinectomy. We did not see evidence of bony resorption in the paranasal sinuses on computed tomography in any of these individuals.

Histopathologic studies showed a progression from abnormalities of pseudostratified epithelium (Fig. 3) to progression to squamous metaplasia (Fig. 4) [10^{••}]. The inflammatory infiltrate was composed of lymphocytes and plasma cells.

Empty nose syndrome

Some authors suggest that 'the empty nose syndrome' is a distinct iatrogenic form of atrophic rhinosinusitis [15]. Computed tomographic findings show a widely patent nose and bony atrophy of the sinus walls. Other features include preoccupation with nasal symptoms, inability to concentrate, fatigue, irritability, anxiety, and depression [15]. However, diagnostic criteria other than 'paradoxical nasal obstruction' despite a widely patent nose and 'surgical removal of nasal turbinates' have been proposed. The relationship of turbinectomy to atrophic rhinosinusitis seems strong, although there is no clear pathophysiologic explanation of how the first process leads to the second. We postulate that loss of humidification of inspired air may lead to a disordered nasal ecology including damage to the respiratory epithelium and

Figure 2 Rhinoscopic views in atrophic rhinosinusitis

Rhinoscopic views in atrophic rhinosinusitis (a) through a nasal septum perforation shows surrounding crusting and bleeding. (b) The right nasal passage reveals a partial middle turbinectomy with dry mucus crusting and surrounding edema. (c) The left nasal passage reveals a large maxillary antrostomy with dry mucus crusting. Reproduced with permission from [10**].

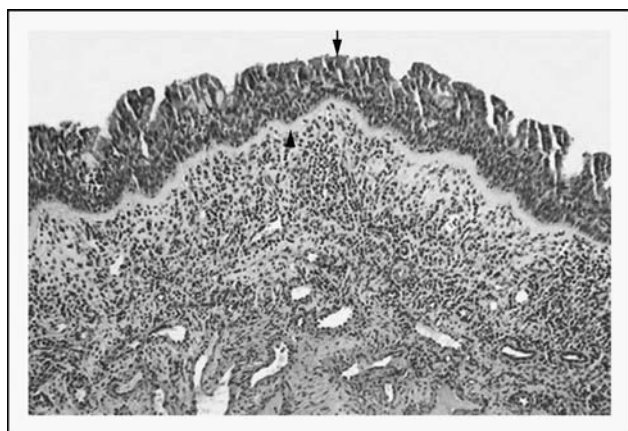
changes in mucous initiating a cascade of pathogenic effects. Others suggest that there is inadequate evidence for the differentiation of this syndrome from secondary atrophic rhinitis [16*].

Animal models

Progressive atrophic rhinitis (PAR) is a highly prevalent, contagious respiratory disease of swine that occurs world-

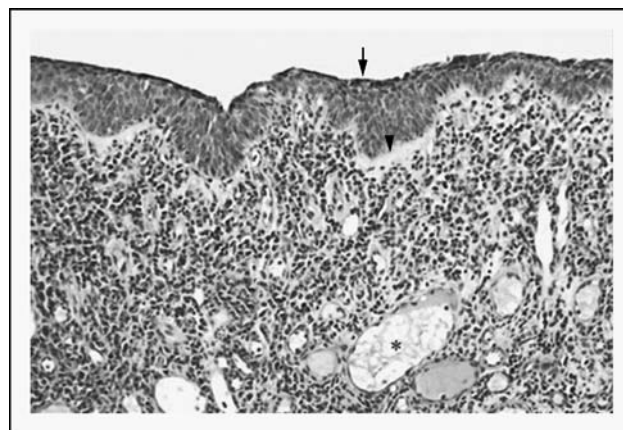
wide [17]. The disease has caused major economic losses in the swine industry. It appears to be the swine equivalent of PAR. Among many bacterial pathogens colonizing the nasal cavity and tonsils of pigs, *Pasteurella multocida*, alone or in combination with *Bordatella*

Figure 3 Normal respiratory epithelium with areas of the pseudostratified epithelium devoid of goblet cells (arrow) and thickened basement membrane (arrowhead)



Original magnification 120. Reproduced with permission from [10**].

Figure 4 Nonkeratinizing squamous metaplasia (arrow) of the normal respiratory epithelium with complete loss of goblet cells and thickening of the basement membrane (arrow head)



The lamina propria contains dense chronic inflammatory infiltrate composed of lymphocytes and plasma cells. Significant numbers of eosinophils and neutrophils are not identified. Many of the blood vessels in the lamina propria are dilated (asterisk). Original magnification 120. Reproduced with permission from [10**].

bronchiseptica, has been identified as the causal pathogens for this disease. The characteristic signs of PAR in swine include turbinate atrophy, facial distortion, nasal hemorrhage, and subsequent growth retardation (Fig. 5) [18,19^{••}]. Toxigenic strains of *P. multocida* produce a heat-labile exotoxin (PMT) that appears to be the virulence factor responsible for the turbinate atrophy observed in PAR. Inoculation with PMT alone reproduces all major symptoms of PAR including growth retardation in swine [19^{••}].

Pasteurella multocida or *B. bronchiseptica* vaccines have been shown to be effective in reducing the level of colonization by these bacteria and bacterial toxoids made with formaldehyde-inactivated PMT induce a protective immune response against PMT challenge. Recombinant vaccines for PAR are now under development [17].

Management: general

Patients with atrophic rhinosinusitis require lifelong management (given below) [20^{••}].

Management of atrophic rhinosinusitis:

- (1) Diagnosis and treatment of underlying treatable conditions
- (2) Nasal hygiene (irrigation)
- (3) Antibiotics
- (4) Moisturization
- (5) Surveillance rhinoscopy

An undetected inflammatory disorder should be considered if systemic symptoms such as weight loss or shortness of breath are present or if there is chronic epistaxis or septal perforation detected on a complete rhinoscopic examination. In this setting, laboratory evidence may also suggest an underlying inflammatory process. We recommend a complete blood count, complete metabolic profile, rapid plasma regain, HIV, anti-neutrophil cytoplasmic antibody, C-reactive protein,

urine analysis, computed tomogram of the sinuses, and a chest X-ray be obtained as part of the initial action. We do not obtain nasal cultures unless primary atrophic rhinosinusitis is in the differential diagnosis as they are predictably positive for enteric organisms such as *E. coli* which colonize the stagnant mucous in the secondary form.

A nasal biopsy should be obtained if there is a question of secondary atrophic rhinosinusitis due to an underlying inflammatory process such as sarcoidosis. Depending on the patient's history, examination for fungus, acid fast mycobacterium, spirochetes, or granulomatous changes may be helpful. In our experience with the secondary form of the disease, it seems to 'burn out' spontaneously in a subset of patients. This leaves them with a dry, crusty nose thereafter.

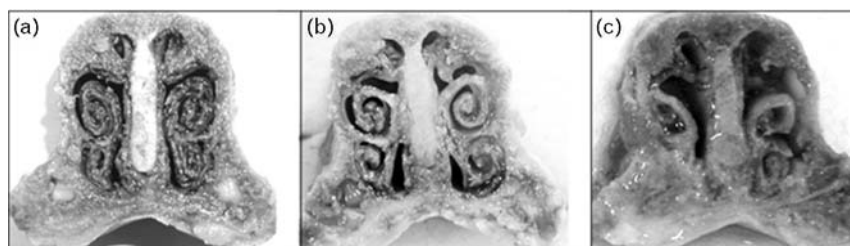
Nasal hygiene

Controlled trials evaluating therapies for atrophic rhinosinusitis have not been performed, with only observational and case studies reporting efficacy. Our approach to management of atrophic rhinosinusitis is, therefore, empiric. Daily therapy includes nasal lavage and lubrication. Topical antibiotics are added when indicated and any active underlying disease process is treated if present (given below) [21].

Nasal irrigation in atrophic rhinosinusitis (from [21]):

- (1) Daily nasal irrigations with normal or hypertonic saline (maximum of 200 ml lavage for each nares).
- (2) Inclusion of a corticosteroid as a terminal component of the lavage is often helpful [one ampule of budesonide respule (0.25 mg/2 ml) in 50 ml of lavage to each nares at the end of the saline lavage, twice a day, is the usual dose].
- (3) Empiric irrigation with a topical nasal antibiotic is used when purulence is detected in the saline lavage (50 ml lavage to each nares after saline irrigation twice a day).

Figure 5 Cross-sections of turbinate bone tissue from (a) control pig, (b) pig challenged with *B. bronchiseptica* after immunization, and (c) a un-vaccinated pig challenged with *B. bronchiseptica* demonstrating atrophic rhinosinusitis



Reproduced with permission from [18].

Some concentrations recommended include the following:

- (1) Bactroban: 5 g ointment (ointment, not nasal ointment or cream) in 1000 ml normal saline. May be stored at room temperature.
- (2) Levofloxacin: 400 mg in 1000 ml of normal saline. Refrigerate. Use entire solution in 14 days or less.
- (3) Ceftazidime: 1 g in 1000 ml of normal saline. Refrigerate. Use entire solution in 10 days or less.

Nasal lavage is associated with improvement in most types of chronic rhinitis and carries little risk if properly performed, although it has not been specifically studied in the treatment of atrophic rhinosinusitis [22]. Patients with atrophic rhinosinusitis are encouraged to lavage their noses with warmed isotonic saline at least twice daily. We recommend using a Water Pik device with a Grossan tip (Hydro Med, Los Angeles, CA; Kenwood Therapeutics, Fairfield, NJ). Other devices, such as bulb syringes, bottle sprayers, and nebulizers are also effective, provided they deliver an adequate volume of solution (>200 ml per side) into the nose. After lavage, we use one of several agents to lubricate the mucosa. Acceptable products include petroleum jelly or personal lubricants such as KY Liquid (McNeil PPC, Inc., Skillman, NJ).

Antibiotics

Few data exist concerning the efficacy of antibiotics added to lavage solutions in atrophic rhinosinusitis. However, case reports and small series of patients with recalcitrant rhinitis from various causes have found the intervention helpful [21,23]. Theoretically, lavage with antibiotic solutions provides relatively high concentrations of drug directly to the nasal cavity, which is the primary site of the pathology in atrophic rhinosinusitis, and to the sinuses as well.

An antibiotic may be added to the lavage when the nasal wash or nasal discharge becomes persistently purulent for more than 2 days (see above) [21]. We use mupirocin initially. The antibiotic solution is used twice daily until the patient no longer notes purulent nasal discharge and/or purulence clears from the lavage solution.

The oral administration of antibiotics may also be required for acute infections with systemic symptoms. We generally use quinolones or other broad-spectrum antibiotics, although there are no specific studies examining choice of antibiotics in this situation. Recurrent oral antibiotic administration leads to progressively more antibiotic resistance of the enteric organisms superinfecting the nasal mucinous.

Surveillance rhinoscopy (with a nasal endoscope) is performed to remove synechiae or excessive crusting at least

twice a year as long as symptoms persist. This should be performed by an otolaryngologist or other physician trained in endoscopic rhinoscopy, as excessive bleeding may result if the procedure is improperly done.

A number of surgical procedures for treatment of atrophic rhinosinusitis have been proposed. However, controlled trials have not been performed to adequately assess their efficacy. These include temporary closure of the nostrils to facilitate regrowth of the nasal epithelium (Young's operation), surgical implantation of acrylic, Teflon, silastic, or polyethylene materials to form a lattice for tissue regrowth, flap procedures, injection of allogeneic bone or fat, and injection of placental tissue. Without appropriate scientific scrutiny these procedures are not recommended unless as part of controlled scientific trials.

Conclusion

Multicenter studies using recently published diagnostic criteria for secondary atrophic rhinosinusitis are required to obtain more information on the specific pathogenesis and optimal treatment. The role of surgical turbinate resection as a cause of this syndrome is important and also requires further study.

Acknowledgements

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 64).

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