

Chronic granulomatous diseases in Otorhinolaryngology – Revisiting the malady

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Received: 4th September 2026; **Accepted:** 21st September 2026; **Published:** 01st October 2026

Introduction

Chronic granulomatous diseases (CGDs) of the head and neck present an enduring diagnostic and therapeutic challenge in contemporary otolaryngology [1-3]. Encompassing infectious etiologies such as rhinoscleroma, mycobacterial tuberculosis, and invasive fungal infections, alongside autoimmune entities including granulomatosis with polyangiitis (GPA), these conditions frequently masquerade as sinonasal malignancies or recalcitrant chronic rhinosinusitis [1,4-6].

Despite modern advancements in molecular diagnostics, immunohistochemistry, and targeted pharmacotherapy, clinical pitfalls such as delayed presentation, extensive tissue destruction, pseudoepitheliomatous hyperplasia, and high rates of cicatricial recurrence persist particularly across endemic regions [1,2,7-8]. This editorial comprehensively revisits the pathophysiological spectrum, microenvironmental mucosal immunology, diagnostic dilemmas, modern therapeutic algorithms, and surgical paradigms in chronic granulomatous disorders of the upper aerodigestive tract [1-10]. It emphasizes the clinical imperative for early, representative deep-tissue histopathological confirmation and individualized, interdisciplinary multimodal management [4, 6, 10].

The Enduring Diagnostic Dilemma:

Chronic granulomatous diseases (CGDs) in otolaryngology encompass a broad and heterogeneous spectrum of infectious, inflammatory, and autoimmune disorders

characterized histologically by organized, compact collections of epithelioid histiocytes, multinucleated giant cells, and surrounding mature lymphocytes [5-6]. Despite historical assumptions that many of these infectious entities had faded into clinical obscurity or remained strictly confined to socioeconomically disadvantaged populations, CGDs continue to pose a formidable challenge to modern otorhinolaryngologists worldwide [1, 5, 9].

The head and neck region, with its exceptionally dense vascularity, expansive mucosal surfaces, and continuous exposure to ambient environmental pathogens, serves as both a primary portal of entry for airborne microorganisms and a target organ for systemic immunologic vasculitides [6-7]. Clinical manifestations span a vast spectrum: from subtle, non-specific nasal crusting, hyposmia, and indolent mucosal ulceration to catastrophic cartilaginous destruction, orbital extension, cranial neuropathy, and life-threatening subglottic stenosis [1, 2, 7].

The core clinical dilemma of CGDs lies in their extraordinary capacity for diagnostic mimicry [1, 6, 10]. In their early, insidious phases, granulomatous lesions are easily misdiagnosed as allergic rhinitis, rhinosinusitis with nasal polyposis, or simple benign nasal septal perforations. In their late, aggressive, or cicatricial phases, they closely simulate aggressive sinonasal malignancies such as inverted papillomas, squamous cell carcinomas, NK/T-cell lymphomas, or

olfactory neuroblastomas [2, 8, 10]. Diagnostic confusion frequently yields disastrous consequences: either inappropriate, radical surgical exenteration executed for a primarily medical pathology or, conversely, aggressive systemic immunosuppressive therapy inadvertently administered to an unrecognized, rampant infectious pathogen [6,8].

Revisiting this clinical malady is imperative [1]. Shifts in global human migration, the rising prevalence of secondary immunodeficiencies, evolving multi-drug antimicrobial resistance patterns, and the post-pandemic emergence of severe fungal sequelae necessitate a renewed diagnostic vigilance and standardized, evidence-based management algorithms [3,4,8].

Pathophysiological Spectrum and Immunological Dynamics:

Granulomatous inflammation represents a specialized host tissue response a delayed (Type IV) cell-mediated hypersensitivity reaction designed to isolate and wall off persistent, poorly soluble organic or inorganic antigens that host neutrophils and non-activated macrophages have failed to eradicate [5-6]. Characterizing the underlying immunological architecture is vital to differentiating infectious from non-infectious autoimmune pathologies [6-7].

1. Infectious Granulomatous Diseases:

- *Rhinoscleroma*: Caused by the Gram-negative encapsulated bacillus *Klebsiella pneumoniae* subsp. *rhinoscleromatis*, this chronic inflammatory disease typically progresses through three distinct, overlapping clinical phases [1,2,5,9]:
 - a) *Atrophic (Catarrhal) Phase*: Characterized by foul-smelling purulent rhinorrhea, marked mucosal atrophy, and heavy nasal crusting that clinically mimics primary rhinitis ozaena [1,9].
 - b) *Granulomatous (Nodular) Phase*: Non-tender, bluish-red mucosal nodules expand within the nasal septum, inferior turbinates, nasopharynx, and exonasal soft tissues [2,9]. Histopathologically, this phase reveals pathognomonic Mikulicz cells (large, vacuolated histiocytes containing viable intracellular bacilli) alongside Russell bodies

(eosinophilic, immunoglobulin-dense plasma cells) [1,5,9].

- c) *Cicatricial Phase*: Dense fibrotic tissue replaces active granulomas, resulting in severe concentric stenosis of the anterior nares, soft palate distortion, and laryngeal occlusion [1-2].

- *Mycobacterial Infections*: Extrapulmonary tuberculosis involving the sinonasal tract, middle ear cleft, and larynx is increasingly recognized [6]. Laryngeal tuberculosis, presenting with hoarseness, odynophagia, and exophytic lesions, exhibits classic caseating granulomas with Langhans-type giant cells [6, 10].

- *Fungal Granulomatous Pathologies*: Chronic invasive fungal rhinosinusitis driven by *Aspergillus*, *Mucorales*, or dematiaceous species presents with tissue necrosis, vascular thrombosis, and variable granulomatous reactions, requiring rapid identification to prevent intracranial or intraorbital dissemination [3, 8].

2. Autoimmune and Idiopathic Entities:

- *Granulomatosis with Polyangiitis (GPA / Wegener's)*: Over 80% to 90% of GPA patients exhibit otolaryngologic manifestations during their disease course [7]. Pathologically defined by necrotizing granulomatous vasculitis of small-to-medium blood vessels, clinical signs include bloody nasal crusting, saddle nose deformity secondary to septal cartilage destruction, serous otitis media, and subglottic stenosis [6-7]. Circulating cytoplasmic antineutrophil cytoplasmic antibodies targeting proteinase-3 (c-ANCA / PR3-ANCA) serve as the primary diagnostic biomarker [7].
- *Sarcoidosis*: A systemic non-caseating granulomatous disease affecting the sinonasal mucosa, larynx, and salivary glands [6]. Endoscopically, sinonasal sarcoidosis presents with yellow-tinted mucosal nodules ("cobblestoning"), friability, and bone erosion [6, 10].

- *Eosinophilic Granulomatosis with Polyangiitis (EGPA / Churg-Strauss)*: Characterized by asthma, severe allergic rhinitis, peripheral blood eosinophilia, and necrotizing vasculitis, with positive perinuclear ANCA (p-ANCA / MPO-ANCA) in a subset of patients [6-7].

Diagnostic Traps and the Pitfall Matrix:

Reaching an accurate diagnosis in chronic granulomatous ENT disorders is laden with diagnostic hazards [6, 10]. Reliance on superficial mucosal sampling or isolated blood investigations frequently precipitates clinical misdirection [6,10].

Critical Diagnostic Pitfalls:

- *The "Superficial Biopsy" Trap*: Biopsies taken from superficial necrotic debris or ulcerated surfaces harvest only inflammatory slough, masking the diagnostic deep-seated granulomas in the submucosa or periosteum [6,10].
- *Pseudoepitheliomatous Hyperplasia (PEH)*: Long-standing mucosal inflammation in conditions like rhinoscleroma can induce dramatic PEH in the overlying epithelium [1,9]. Unaware pathologists may misinterpret PEH as well-differentiated squamous cell carcinoma, leading to unnecessary radical surgical resection [1,6].
- *Serological Ambiguity*: While c-ANCA positivity strongly suggests GPA, low-level titers can occur secondarily in active tuberculosis or chronic fungal infections [6,7]. Conversely, "limited" head and neck GPA remains seronegative in up to 30% of cases [7].
- *Steroid Pre-treatment Blinding*: Empirical administration of systemic steroids prior to tissue biopsy blunts granulomatous architecture, blurs histological detail, and risks accelerating undiagnosed fungal or mycobacterial infections [3,8].

Recommended Diagnostic Algorithm:

- *Generous Deep Biopsies*: Multiple biopsies must be harvested from the active, non-necrotic margin of the lesion, reaching into the submucosa [6,10].

- *Histochemical Battery*: Specimens must undergo routine H&E staining alongside special stains: Periodic Acid-Schiff (PAS) and Grocott's Methenamine Silver (GMS) for fungi, Ziehl-Neelsen (ZN) for acid-fast bacilli, and Gram stain for bacteria [3, 5-6].
- *Fresh Tissue Cultures*: Unfixed tissue must be submitted directly for aerobic, anaerobic, fungal, and mycobacterial cultures, alongside quantitative Polymerase Chain Reaction (PCR) assays [3, 5, 8].
- *Advanced Imaging*: High-resolution non-contrast CT evaluates osteonecrotic patterns and bony erosion, while contrast-enhanced MRI assesses soft-tissue extension, dural involvement, and perineural spread [6, 8].

Modern Management Paradigms:

Medical versus surgical interventions managing chronic granulomatous ENT disorders demands strict disease-specific strategies [1,3,7]. Treating an undiagnosed infectious granuloma with systemic immunosuppressants can trigger fatal dissemination, whereas treating autoimmune vasculitis solely with antibiotics guarantees progressive tissue necrosis [6,7].

Surgical Philosophy:

From Radical Resection to Functional Restoration. Historically, many granulomatous diseases were managed with aggressive resections [1, 8]. Modern otolaryngology emphasizes a conservative, endoscopic approach focused on three primary pillars [1, 6, 8]:

1. *Airway Security*: In cases of severe laryngotracheal or exonasal stenosis (particularly in advanced rhinoscleroma or GPA), surgical priority focuses on maintaining airway patency [1,2,7]. Techniques include endoscopic coblation, balloon dilation, and stent placement (such as rubber tube recanalization) to preserve mucosal integrity while avoiding formal open tracheostomy when possible [1,2,9].
2. *Targeted Debridement*: Removing devitalized bone, necrotic tissue, and

fungal sequestra reduces bacterial/fungal burden and restores sinus ventilation without disrupting uninvaded structural frameworks [3,8].

3. *Reconstructive Timing:* Reconstructive procedures (e.g., septorhinoplasty for saddle nose deformity or microvascular free tissue transfer for palatal defects) must be strictly delayed until the patient achieves sustained, documented clinical, serological, and histological remission for a minimum of 6 to 12 months [6-7]. Early reconstructive intervention in an actively inflamed field leads to graft loss, wound dehiscence, and disease flare-ups [6-7].

Financial Support and sponsorship: Nil

Conflicts of interest: There are no conflicts of interest.

Conclusion and Call to Action

Chronic granulomatous diseases in otolaryngology represent an intricate intersection of microbiology, immunology, and surgical skill [1, 6]. As emerging pathogens, post-viral infectious sequelae, and diagnostic nuances complicate the clinical landscape, otolaryngologists must maintain a high index of suspicion when encountering recalcitrant mucosal disease [3, 4, 10]. Bridging the gap between early histopathological identification, prudent antimicrobial or immunomodulatory therapy, and conservative surgical restoration remains key to taming this persistent malady [1, 3, 7].

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Cite this article as: Belaldavar BP. Chronic granulomatous diseases in Otorhinolaryngology – Revisiting the malady. *Al Ameen J Med Sci* 2026; 19(4):261-264.

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