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Rhinotopic Therapy for Atypical Mycobacterial Infections of the Sino-Nasal Tract: Case Report and Review of the Literature

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Abstract

Atypical *mycobacterium* is unusual causes of refractory Chronic Rhinosinusitis (CRS) and there is no universally accepted therapeutic regimen for this disease in the otolaryngology literature. Treatment can be a challenge as resistance to oral antibiotics often develops with time, necessitating long-term intravenous antibiotics which carry the risk of significant morbidity. We present a case of refractory CRS secondary to *Mycobacterium abscessus* in an immunocompetent patient. The organism was resistant to oral macrolides and the patient declined intravenous antibiotics. He was successfully treated with a long-term topical sinus therapy regimen that we had previously developed for refractory bacterial CRS (the "rhinotopic protocol") and remained disease free for a period of four years. Topical therapy can provide mucosal antibiotic levels which are above the required minimal minimum bactericidal concentration, without the risks of systemic toxicity. Rhinotopic therapy can be a valuable option in refractory CRS caused by multi-resistant atypical mycobacteria.

Keywords: Chronic rhinosinusitis; Atypical mycobacteria; *Mycobacterium abscessus*; Rhinotopic therapy

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Introduction

Atypical Mycobacteria (AM), also referred as nontuberculous *mycobacterium*, is a subgroup of mycobacteria other than the *mycobacterium tuberculosis* and *mycobacterium leprae* complex which are droplet and contact borne. These are ubiquitous, widely distributed in nature, being found in the soil, sewage, household pluming, drinking and distributing water unpasteurized milk, and animals [1]. They usually have a low infectious potential, primarily affecting immunocompromised individuals, although infections in immunocompetent individuals have been reported [2,3]. In 1959 Runyon classified AM into 4 groups based primarily on their pigmentation and growth rate, and to date over 50 species have been identified to cause disease in humans [4]. AM disease has been described with skin and soft tissue infections, osteomyelitis, lung disease both in immunocompromised and immunocompetent individuals.

Sino-nasal infections are rare with only about a hundred cases reported, however this is probably an under diagnosis as AM needs special staining to be visualized and specific culture media to be grown [5]. When the sinuses are involved, the patients' signs and symptoms are somewhat similar to those of run-of-the-mill bacterial Chronic Rhinosinusitis (CRS) and the only way to confirm this by biopsy and culture [6]. One of the important characteristics of AM is their resistance to numerous antibiotics, which can make treatment difficult and prolonged [7]. The American Thoracic Society/ Infectious Diseases Society of America (ATS/IDSA) typically recommends an oral macrolide-based treatment regimen (such as clarithromycin) based on susceptibility testing, for a duration of several months and the ATS/IDSA guidelines state that there are no particular drug combinations with definitely proven efficacy [8]. Oral macrolides are the most widely prescribed antimicrobials however resistance often occurs over time, which significantly complicates treatment [9]. Only about 50% of *Mycobacterium abscessus* strains are susceptible to oral clarithromycin; moreover, complications are not unusual and 15% to 20% of patients experience significant gastrointestinal side-effects [10]. The problem is that clinicians often find themselves in a situation where various options for oral antibiotics therapy have been exhausted with the only available recourse being long-term intravenous antibiotics, such as amikacin, which carries significant potential toxicity. We report a case of refractory *Mycobacterium abscessus* CRS which was resistant to oral clarithromycin. The patient declined intravenous amikacin and was successfully treated with a rhinotopic regimen

which we had previously used successfully for refractory bacterial CRS [11-13]. Rhinotopic therapy offers an effective and safe alternative to intravenous antibiotics for the treatment of *Mycobacterium abscessus* CRS.

Case Presentation

A 68-years-old male patient presented to our institution with refractory CRS secondary to *Mycobacterium abscessus*. His symptoms started seven months prior to arrival following an open facial and nasal trauma that necessitated lip suturing and septoplasty. The wound was contaminated by dirt and soil. His symptoms consisted of tenacious facial pain and pressure, nasal congestion, and thick chronic postnasal drip. The patient underwent functional endoscopic sinus surgery at an outside institution 4 months prior to coming to us; both pathology and culture showed evidence of mucosal *Mycobacterium abscessus* infection. The organism was initially susceptible to oral macrolides and the patient was treated with oral azithromycin for a period of 6 weeks, however his symptoms persisted. He was subsequently shifted to oral clarithromycin for however he failed to improve after 2 months of treatment, and a repeat Sino-nasal culture reconfirmed the pathogen. By then, the organism had become resistant to both above oral macrolides, and it was susceptible only to parenteral Amikacin, to a lesser extent Ceftazidime, and oral Linezolid. The patient tried a course of oral Linezolid but he had to discontinue it after 10 days due to severe gastrointestinal side effects. At this point his treating physician recommended intravenous amikacin for a minimum of 6 months. The patient declined because of the concern about potential nephrotoxicity and ototoxicity; moreover, he was reluctant to have an indwelling PICC line catheter for such a prolonged period. He sought multiple second opinions at different institutions across the country and he was consistently advised that a 6 month-course of intravenous antibiotics was the only remaining option. He decided to come to our institution, having done some research online, specifically requesting to try the rhinotopic protocol which we had developed and found to be effective against refractory bacterial CRS [11-13]. Upon initial nasal endoscopy severely inflamed mucosa and infected debris were noted in both ethmoid and maxillary sinus cavities. Computed tomography of the sinuses showed significant mucosal thickening of the maxillary, ethmoid and sphenoid sinuses, with blockage of the sinus Ostia bilaterally, worse on the right side (Figure 1). In-office biopsy was sent for histopathology and culture and both confirmed persistent *Mycobacterium abscessus*, with a similar resistance profile as previously. The patient underwent revision bilateral spheno-ethmoidectomy with opening of the frontal obstruction and removal of all visible infected granulation-like tissue under navigation guidance. All sinus Ostia were widely opened in order to provide adequate access for topical medications, which we feel is crucial for the success of rhinotopic therapy. Histopathology revealed inflamed sinus mucosa with non-caseating granulomas. The culture re-confirmed the presence of *Mycobacterium abscessus*, with the exact same sensitivities (Figure 2).

The patient was started on the rhinotopic protocol, which consisted of twice-a day nasal nebulization of amikacin (150 mg), ceftazidime (600 mg), and betamethasone (0.5 mg), which he did at home using a commercial nebulizer. He also rinsed his sinus cavities twice daily with nasal saline using the NeilMed bottle. In addition, he had weekly in-office intra-sinus administration of polaxamer gel which was pre-loaded with amikacin (60 mg/ml), ceftazidime (30 mg/ml) and mometasone (240 mcg/ml). Poloxamer are macro-polymeric

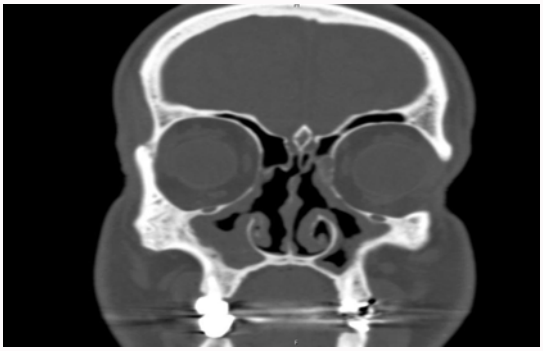

Figure 1:

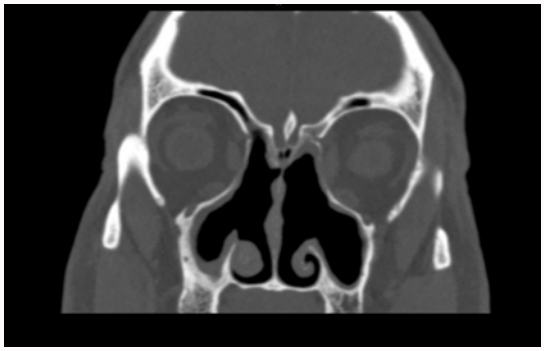

Figure 2:

substances composed of bifunctional triblock copolymers which incorporate both lipophilic (poly-propylene oxide) and lipophobic (polyethylene oxide) residues. The gel is liquid at room temperature and becomes more viscous and mucoadhesive as it gets warmer with body temperature after being placed in the sinus cavity (hence the term "thermoreversible"). This feature allows it to be retained longer in the sinus cavity and prevents its rapid removal by the continuous mucociliary beating. The gel-containing syringes are prepared for us by a regional formulating pharmacy and we apply the gel in the office under endoscopic visualization so that to ensure correct placement inside the sinus cavities. Typically, 3 milliliters of gel are applied on each side, divided equally between the fronto-ethmoidal, sphenoethmoidal and maxillary areas.

The patient initial pre-treatment Lund Kennedy scores and Lund Mackay scores dropped from 12 and 14 respectively, down to 0 and 2 at 6 weeks, and treatment was continued for 6 months, which would correspond to the standard parenteral therapy duration. He continued to improve being followed clinically and we followed him regularly every 2 months, with nasal endoscopy showing persistently healthy sinuses at one year. Two endoscopically guided in-office maxillary biopsies were done at 6 months and 12 months and both revealed negative culture. He remained symptom free for a period of 4 years and was followed up by his hometown otolaryngologist in Florida; he continued to visit our practice in Maryland three times a year. After 4 disease-free years, he started noticing recurrence of mild nasal congestion and PND, but he had no sinus pain or headaches. A biopsy and culture showed recurrence of the *Mycobacterium abscessus* and he resumed, and then completed, the same Rhinotopic regimen and all his symptoms cleared. He remains disease free since them, which are about for one year following treatment completion, and five years following his initial diagnosis.

Discussion and Literature Review

CRS is a group of complex inflammatory disorders each with unique pathphysiologic factors and phenotypes, rather than a simple infectious disease. Nowhere is the interplay between host, environmental and disease-related factors clearer than in refractory CRS. Rhinosinusitis due to AM is its own special class of resistant sinusitis disease. Even though AM infections are well described in the literature and well recognized in conjunction with lymphadenitis, chronic bronchopulmonary disease, cutaneous/soft tissue disease, osteomyelitis, surgical site infections, and foreign body-related infections, the association of rhinosinusitis with AM is relatively uncommon and often remains unrecognized and under-diagnosed [1,2,4]. Atypical mycobacteria should be considered when CRS patients are refractory to standard medical and surgical treatment, especially if they are immunocompromised, or in the presence of foreign body, trauma or surgical implants nasal, soil or dirt exposure [14-16]. The treating physician should keep in mind though that the disease can happen in immunocompetent patients. Most existing literature consists of isolated case reports, with a few series. The largest reported series was conducted by Solyar et al. [16] and comprised of 37 patients, with only 10 patients having significant risk factors (these included a history of chemo radiation, immune-dysfunction and foreign body). Another smaller case series of 8 patients was reported by Suh et al. [17] with only 3 having significant risk factors (cystic fibrosis and Wegener's granulomatosis). One common risk factor uniformly noted in many patients was a history of prior endoscopic sinus surgery (this was present in 91.3% of the patients) [16].

The clinical symptoms of AM rhinosinusitis are similar to those of any run-of-the-mill bacterial refractory sinusitis. The larger case series reported presenting the symptom to be chronic postnasal discharge (88%), decreased smell and taste (63%), and facial pain/pressure (38%). All patients were noted to have purulence on endoscopy [16,17]. The diagnosis is established through microbiological identification of AM. This can be made difficult by the fact that *mycobacterium* species requires special culture media and takes a long time to grow (often 6 weeks or more) before the diagnosis and antibiotic sensitivities are obtained. Solyer et al. [16] identified 6 different AM species, most frequently *M. abscessus* (57.1%), followed by *M avium*-intracellulare complex (14.3%), *M chelonae* (14.3%), *Mycobacterium mucogenicum* (6.1%), *Mycobacterium avium*-kansasii (4.1%), and *Mycobacterium neoaurum* (2.0%) using both the AFB culture and AFB probe method to confirm speciation. Others have identified *Mycobacterium chelonae* as a common organism [17].

Infections caused by AM are often difficult to treat and require multiple antimicrobial agents for an extended duration, and these mycobacteria multiply slowly and are typically resistant to most currently available antimicrobial agents, including anti-tuberculosis drugs. The treating physician should keep in mind that in vitro drug susceptibility testing does not always correlate to in vivo clinical response [18]. Various AM, including *Mycobacterium abscessus*, often develop Inducible Resistance (IR) to macrolides, which makes these less efficacious. This may be due to the presence of the novel erm (41) gene. Another complicating factor is the fact that MICs or inducing erm (41) could differ according to the type of macrolides [19]. Oral macrolide therapy remains the most commonly employed approach. Solyer et al. [16] described using systemic macrolide therapy in 62% of their series, (10 of them were treated with azithromycin, 12 with clarithromycin), with an average treatment duration of 13.4 weeks (ranging between 2 weeks and 52 weeks). Clinical improvement was noted in 61.9% patients, based on symptoms improvement (sinonasal edema, pus and crusting) and on endoscopic findings [16]. Other authors reported an improvement rate of 73% to 75% with treatment ranging from 6 weeks to 13 months [16,17,20]. In pulmonary disease due to AM, the American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA) recommend a combination therapy of two agents for at least 12 months with continuation of even after obtaining a negative culture [8]. It would be tempting to adopt similar guidelines for sinus disease [21].

To date, there is no standardized treatment for CRS caused by AM. We decided to treat our patient with the rhinotopic protocol using a combination of antimicrobials to treat the infection, and corticosteroid to treat the inflammation. We had not treated CRS due to *Mycobacterium abscessus* in the past, however had extensive prior experience viously with this protocol to for refractory bacterial CRS [11-13,22-25]. We favor the thermo-reversible polaxamer gel which is liquid at refrigerated temperatures and which becomes for viscous and mucoadhesive as it settles in the more warm sinus cavities, as this prevent it from rapidly cleared by the mucociliary system of the sinuses. Our patient responded well to this topical therapy protocol and was able to tolerate the prolonged treatment without any complications. More importantly, we were able to avoid the need for an indwelling PICC line and the significant potential side effects of prolonged parenteral amikacin. The treatment can be repeated in case of disease recurrence. We stress the importance of a widely opening the sinuses through a complete endoscopic sinus surgery to allow adequate access of the medications to the target mucosa.

Conclusion

Topical therapy can provide mucosal antibiotic levels which are above the required minimal minimum bactericidal concentration, without the risks of systemic toxicities. The rhinotopic protocol may offer a valuable treatment option for refractory CRS caused by multi-resistant atypical mycobacteria.

References

1. Wagner D, Young LS. Nontuberculous mycobacterial infections: A clinical review. Infection. 2004;32(5):257-70.

2. Williams MM, Yakrus MA, Arduino MJ, Cooksey RC, Crane CB, Banerjee SN, et al. Structural analysis of biofilm formation by rapidly and slowly growing nontuberculous mycobacteria. Appl Environ Microbiol. 2009;75(7):2091-8.

3. Spring PM, Miller RH. Initial report of primary sinusitis caused by an atypical pathogen (Mycobacterium chelonae) in an immunocompetent adult. Ear Nose Throat J. 1999;78(5):358-9,362-4.

4. Runyon EH. Anonymous mycobacteria in pulmonary disease. Med Clin North Am. 1959;43(1):273-90.

5. Mushatt DM, Witzig RS. Successful treatment of mycobacterium abscessus infections with multidrug regimens containing clarithromycin. Clin Infect Dis. 1995;20(5):1441-2.

6. McCoul ED, Tabaee A. A practical approach to refractory chronic rhinosinusitis. Otolaryngol Clin North Am. 2017;50(1):183-98.

7. Brown BA, Wallace RJ Jr, Onyi GO, De Rosas V, Wallace RJ III. Activities of four macrolides, including clarithromycin, against Mycobacterium fortuitum, Mycobacterium chelonae, and M. chelonae-like organisms. Antimicrob Agents Chemother. 1992;36(1):180-4.

8. Griffith DE, Aksamit T, Brown-Elliott BA, Catanzaro A, Daley C, Gordin F, et al. An official ATS/IDSA statement: diagnosis, treatment, and

prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med. 2007;175(4):367-416.

9. Lin SS, Lee CC, Jang TN. Soft tissue infection caused by rapid growing Mycobacterium following medical procedures: Two case reports and literature review. Ann Dermatol. 2014;26(2):236-40.
10. Periti P, Mazzei T, Mini E, Novelli A. Adverse effects of macrolide antibacterials. Drug Saf. 1993;9(5):346-64.
11. Shikani AH, Kourelis K, Alqudah MA, Shikani HJ, Cope E, Kirk N, et al. Multimodality topical therapy for refractory chronic rhinosinusitis: Our experience in thirteen patients with and twelve patients without nasal polyps. Clin Otolaryngol. 2013;38(3):254-8.
12. Shikani AH, Jabra-Rizk MA, Shikani HJ, Basaraba RJ, Leid JG. Rhinotopic therapy for refractory rhinosinusitis: Clinical effectiveness and impact on the epithelial membrane and mucosal biofilms. J Otol Rhinol. 2015;4(5).
13. Shikani AH, Khoueir N, Jabra-Rizk MA, Shikani HJ, Basaraba RJ, Leid JG. Topical therapy for refractory rhinosinusitis caused by methicillin-resistant Staphylococcus aureus: First report in a prospective series. Auris Nasus Larynx. 2018;45(5):994-9.
14. Tichenor WS, Thurlow J, McNulty S, Brown-Elliott BA, Wallace RJ, Falkinham JO. Nontuberculous Mycobacteria in household plumbing as possible cause of chronic rhinosinusitis. Emerg Infect Dis. 2012;18(10):1612-7.
15. Prokopakis E, Nikolaou V, Vardouniotis A, Jorissen M. Nasal manifestations of systemic diseases. B-ENT. 2013;9(3):171-84.
16. Solyar A, Lee AS, Przybyszewski B, Lanza DC. Atypical mycobacterium detection in refractory chronic rhinosinusitis. Otolaryngol Head Neck Surg. 2012;146(6):1012-6.
17. Suh JD, Ramakrishnan VR, Tajudeen B, Reger C, Kennedy DW, Chiu AG. Identification and treatment of nontuberculous Mycobacterium sinusitis. Am J Rhinol Allergy. 2011;25(6):421-4.
18. Kim SY, Kim CK, Bae IK, Jeong SH, Yim JJ, Jung JY, et al. The drug susceptibility profile and inducible resistance to macrolides of Mycobacterium abscessus and Mycobacterium massiliense in Korea. Diagn Microbiol Infect Dis. 2015;81(2):107-11.
19. Choi GE, Shin SJ, Won CJ, Min KN, Oh T, Hahn MY, et al. Macrolide treatment for Mycobacterium abscessus and Mycobacterium massiliense infection and inducible resistance. Am J Respir Crit Care Med. 2012;186(9):917-25.
20. Walsh JC, Tichenor WS. Atypical mycobacteria as a cause of chronic sinusitis. J Allergy Clin Immunol. 2008;121(2):S264.
21. Shikani A, Chahine K, Alqudah M. The rhinotopic therapy protocol for chronic refractory rhinosinusitis: How we do it. Clin Otolaryngol. 2010;35(4):329-32.
22. Jeon K, Kwon OJ, Lee NY, Kim BJ, Kook YH, Lee SH, et al. Antibiotic treatment of Mycobacterium abscessus lung disease: A retrospective analysis of 65 patients. Am J Respir Crit Care Med. 2009;180(9):896-902.
23. Shikani AH, Chahine KA, Alqudah MA. Rhinotopic therapy for refractory chronic rhinosinusitis: A study of 20 cases. Ear Nose Throat J. 2014;93(4-5):E48-54.
24. Shikani AH, Kourelis K, Rohayem Z, Basaraba RJ, Leid JG. Topical gel therapy for sinonasal polyposis in Samter's triad: preliminary report. Ann Otol Rhinol Laryngol. 2012;121(11):719-24.
25. Shikani A, Kourelis K. Topical membrane therapy for chronic rhinosinusitis. Peculiar aspects of rhinosinusitis: InTech. 2011;91-112.