

SHORT COMMUNICATION

Chronic rhinosinusitis and psoriasis: do mutually exclusive systemic Th1 and Th2 disease patterns exist?

RASHID M. RASHID¹, ANDREW MILLER³, JOSEPH M. SCIANNA² & JAMES A. STANKIEWICZ²

¹MD PhD Department and ²Department of Otolaryngology-Head and Neck Surgery Loyola University, Maywood, IL and

³Departments of Internal Medicine and Emergency Medicine, State University of New York Downstate Medical Center and Kings County Hospital Center, Brooklyn, NY, USA

Abstract

Conclusion. Our results support the theory that chronic rhinosinusitis (CRS) is a systemic Th alteration, the relevance of which is discussed in detail. **Objective.** CRS imposes a heavy burden on society; however, a reliable CRS therapy has not been found. Developing a better understanding of this pathology will help us in our search for more effective therapies. One question, which is rarely examined, is the possibility of CRS existing as a systemic immune alteration in Th response. Thus, the goal of this study was to examine the occurrence of CRS, a Th2 pathology, with Th1 pathologies such as psoriasis. **Patients and methods.** This study was performed via a retrospective electronic query of our medical center in regards to patients coded with the respective diagnosis. **Results.** Analysis of the data showed that occurrence of CRS rarely coincided with the occurrence of psoriasis and other such Th1 pathologies.

Keywords: Chronic rhinosinusitis, psoriasis, multiple sclerosis, rheumatoid arthritis, Crohn's disease, Th1, Th2

Introduction

Chronic rhinosinusitis (CRS) affects nearly 10% of the population, making this a profoundly costly disease, both financially and personally [1]. A recent flurry of studies have focused on and advanced our understanding of CRS etiology, with theories that include fungal and bacterial insults [2]. While such studies continue to break new ground, our overall approach to CRS therapy has been to control, palliate, or prevent the pathology on a local level.

However, the possibility of CRS existing as systemic disease is slowly becoming more acceptable. Along this thought process, we believe that immune Th alterations could be a central part of CRS. Specifically, we believe that CRS is a systemic and not merely a local Th2 alteration. And, taking into account the established existence of known and opposing Th1 and Th2 cytokine patterns [3,4], we examined CRS patient files at our institution in search of co-morbid Th1 pathologies, such as

psoriasis. We found the co-existence of the Th2 CRS with Th1 pathologies to be almost non-existent. These results will help to stimulate an entirely novel area of studies and debate, while also further progressing our understanding of CRS.

Patients and methods

An electronic query was performed on patients diagnosed at our institute over the past year. The query was done by diagnostic codes entered into Hyperspace (Epic systems, Madison, WI, USA). We specifically focused on CRS and Th1 pathologies. The Th1 pathologies were chosen from diverse fields, such as neurology and rheumatology. The first search was done to establish baseline population numbers for patients diagnosed with either CRS, or our chosen Th1 pathologies of psoriasis, rheumatoid arthritis (RA), Crohn's disease, or multiple sclerosis (MS). Then, records of patients with CRS were separated and searched for diagnosis of psoriasis,

RA, Crohn's disease, or MS. The percent of Th1 diseases coexisting with CRS, a Th2 disease, was then calculated.

Results

Electronic searches showed the following results. Over the past year, 273 patients had a diagnosis of CRS, 483 had psoriasis, 244 had RA, 119 had Crohn's disease, and 180 had MS.

The next query of CRS patients with a second co-morbid diagnosis showed the following. Of the 273 patients with CRS, 3 had psoriasis, 4 had RA, 1 had Crohn's disease, 2 had MS (Figure 1). The percent of Th1 disease coexisting with CRS (Table I) was found to be below the 10% population prevalence of CRS.

Discussion

The two Th responses are defined by the repertoire of cytokines that predominate. Among other cytokines, Th1 is defined by interferon (IFN)- γ and interleukin (IL)-2 secretion, and Th2 by IL-4 and IL-10 secretion [3]. These cytokine patterns tend to be dominant, for example IFN- γ not only induces the generation of its own Th1 subset, but negatively feeds back to inhibit differentiation of the opposing Th2 subset. This presence, and predominance, of one Th response over another is a much discussed phenomenon [4]. Recently the importance of Th alteration in disease processes has been highlighted in a variety of studies. For example, Th deregulation has been found to play significant roles in aneurysm formation [5] and cancer progression [6,7]. The therapeutic implications of understanding and applying the new Th discoveries are even more fascinating. For example, among the works extolling

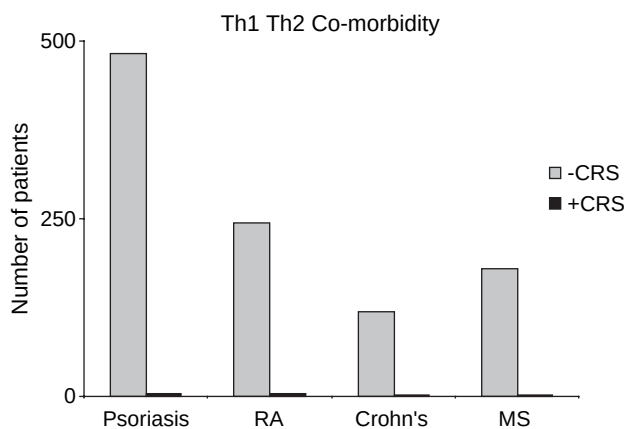


Figure 1. Th1 Th2 co-morbidity. The number of patients with Th1 pathologies, with and without CRS, is noted.

Table I. Co-morbidity of Th1 disease and CRS.

Disease	% of Th1 disease population co-existing with Th2 CRS
Psoriasis	0.6
Rheumatoid arthritis	3
Crohn's disease	0.8
Multiple sclerosis	0.5

this research frontier, are studies that attempt to control allergy by Th-modifying vaccines [8].

CRS is believed to be a predominantly Th2 pathology [9]. Among the evidence, it is known that the mRNA of Th2 cytokines shows increased expression in the sinus mucosa of patients with chronic sinusitis [10]. However, debate remains as to whether the Th response of CRS is a systemic phenomenon or merely an aberrant localized mucosal response isolated to the sinus region [11]. Like certain other groups, we believe our failure to understand the generalized nature of CRS T-cell skewing may be the reason behind our failure to uncover a reliably effective therapy [12]. Our theory espouses the existence of a predominantly systemic Th2 disease with local manifestations. Thus CRS may respond better to systemic, possibly immune modulating therapies, such as those used to manage Th1 pathologies (Table II). In similar supportive examples, asthma patients, who tend to exhibit Th2 cytokine patterns, have been strongly associated with the co-morbidity of CRS [13]. Further extrapolating such findings, reversal of cytokine aberrations have been attempted as a therapeutic approach to asthma and CRS [14]. And although these studies hint at the possibility of systemic Th alterations in CRS [15], our knowledge in this area is still limited. Meanwhile, on the frontier of Th1 pathologies, it is already accepted that the presence of one Th1 pathology is strongly associated with the presence/occurrence of other co-morbid Th1 pathologies [16].

It is well known that certain pathologies (Table III) produce or result from Th alterations but the localized versus systemic nature of these is not yet established [17,18]. As a result, we devised an indirect and interesting exploratory study into CRS and the systemic Th response. As in the previous example of CRS and asthma, we theorized that CRS is secondary to a systemic Th alteration [12]. If so, then the Th alteration may be predominant enough not only to facilitate other Th2 pathologies but also to inhibit systemic Th1 pathologies. Our results show that the presence of CRS does inhibit the presence of Th1 pathologies, suggesting the existence of a very powerful and predominant Th1 response. The opposite is also likely, with the Th1 predominant pathologies inhibiting the occurrence of the Th2

Table II. Immune modulators targeting Th responses.

Immune modulators	Mechanism of action	Th target	Therapeutic use
Abatecept	Inhibits CD28 by binding CD80 and CD86 on antigen-presenting cells	Th1, some Th2	Rheumatoid arthritis
Anakinra	Inhibits IL-1 by binding IL-1 type 1 receptor (IL-1R1)	Th1	Rheumatoid arthritis
Etanercept	Soluble p75 TNF receptor fusion protein (sTNFR-1g)	Th1	Rheumatoid arthritis, psoriasis
Adalimumab	IgG1 monoclonal antibody specific for TNF	Th1	Rheumatoid arthritis, psoriasis
Infliximab	Neutralizes TNF- α	Th1	Rheumatoid arthritis, Crohn's disease, ulcerative colitis, psoriasis
Cyclosporin	Selective IL-2 receptor (CD25) antagonist	Th1, some Th2	Rheumatoid arthritis, psoriasis, transplant rejection, ulcerative colitis
Efalizumab	Anti-CD 11 antibody which inhibits LFA/ICAM (CD11A/CD18) association preventing T-cell activation	Th1, some Th2	Psoriasis
Alefacept (LFA3TIP)	Recombinant human LFA-3/IgG1 fusion protein. Binds CD2 inhibiting LFA-3/CD2 interaction	Th1	Psoriasis
Interferon (IFN)- β -1a/b	May $\downarrow$ B7-1 and $\uparrow$ TNF- β	Th1	Multiple sclerosis

CRS. Regardless of which Th inhibits which, these data further contribute to the currently accumulating literature on Th alterations in CRS.

We further reviewed the literature for similar comorbidity studies. Our search found a few works with somewhat similar but inconclusive reports as discussed below. One study showed a high level of sinonasal disease in patients with Crohn's disease [19], but this is most likely due to an alternate basal airway inflammatory process reported in this patient population [20]. Further supporting our theory is the fact that medically controlling the Th1-predominant Crohn's disease results in the expected counterbalance and emergence of the Th2 sinusitis [21]. In the area of RA, studies have noted an existence of sinonasal disease in RA patients, although authors have further suggested that this phenomenon is most likely an alternate manifestation of RA, and not the traditional Th2 CRS [22,23]. In the area of MS, a retrospective study by Jones et al. found a high incidence of MS and sinonasal disease, but this study involved image analysis and not actual clinical diagnosis of CRS [24]. Regarding the paper by Jones et al., we further suspect the proposed theory that these sinus pathologies are more likely associated with MS flares and resultant decreased host defense mechanisms, such

as physical clearance of the sinuses [25]. Overall, the literature in this area could benefit greatly from increased focus and exploration.

Ultimately, the significance of our results cannot be underestimated. The potential existence of a systemic Th alteration, resulting in secondary CRS, may better guide future studies and therapeutic development. Furthermore, one must wonder, if some patients get CRS and others do not, and this is a systemic disease, then there may also be an inherent genetic predisposition, as has been suggested [26]. Supporting this idea are similar genetic and systemic Th theories accepted as part of Th1 pathologies such as Crohn's disease. Furthermore, we question if the systemic CRS Th response is altered toward an elevated Th2 predisposition or is it a defective or inhibited Th1 that is not providing the counterbalance needed? Finally, can we potentially target and/or immunomodulate the Th response in CRS in a fashion similar to that done in Th1 pathologies [27]?

We acknowledge that this study has limitations. Our intention was to explore and to produce an initial stepping stone upon which further studies could be expanded. Thus, the data collected are reliant, not on the accuracy of specifically designated physicians, but on the diagnostic accuracy of all our institutes' physicians. As a result, many technical and human errors are possible. As a sample, a technician may code a diagnosis incorrectly or a physician may want to spare the patient the cost of a CRS diagnosis and instead charge the visit as a seasonal allergy. But despite these limitations, the clear results do point to a pattern that may be of great potential in future studies of CRS.

Table III. Pathologies by Th predominance.

Th1 diseases	Th2 diseases
Multiple sclerosis	Chronic rhinosinusitis
Rheumatoid arthritis	Allergic rhinitis
Crohn's disease	Atopic dermatitis
Psoriasis	Allergic rhinitis

Finally, in the current study, we attempted to determine the incidence of Th1 pathologies in CRS. From this, we hoped to develop a better understanding of CRS as a systemic Th pathology, and also to allow a platform for future studies. In conclusion, we found the co-occurrence of Th1 disease to be almost non-existent with the predominant Th2 CRS. CRS must, therefore, be a systemic Th2 pathology within the host. A series of studies can be pursued based on this work, as many questions remain to be examined. Ideally, we would like to follow up with the 10 aberrant Th2 cases that did occur with CRS to dig for further clues. For example, knowing what was different about the CRS, or even the Th2 disease in these 10 patients may lead us down new and previously unexplored paths in CRS. We believe that this study will help to increase our understanding of CRS, facilitate further reports on Th co-morbidities, and encourage further discussion and theories on the pathology of CRS and its potential treatments.

References

- [1] Bhattacharyya N. The economic burden and symptom manifestations of chronic rhinosinusitis. *Am J Rhinol* 2003; 17:27–32.
- [2] Elliott KA, Stringer SP. Evidence-based recommendations for antimicrobial nasal washes in chronic rhinosinusitis. *Am J Rhinol* 2006;20:1–6.
- [3] Abbas AK, Murphy KM, Sher A. Functional diversity of helper T lymphocytes. *Nature* 1996;383:787–93.
- [4] Herring AC, Hernandez Y, Huffnagle GB, Toews GB. Role and development of TH1/TH2 immune responses in the lungs. *Semin Respir Crit Care Med* 2004;25:3–10.
- [5] Shimizu K, Libby P, Mitchell RN. Local cytokine environments drive aneurysm formation in allografted aortas. *Trends Cardiovasc Med* 2005;15:142–8.
- [6] Rashid RM, Achille NJ, Lee JM, Lathers DM, Young MR. Decreased T-cell proliferation and skewed immune responses in LLC-bearing mice. *J Environ Pathol Toxicol Oncol* 2005; 24:175–92.
- [7] Lathers DM, Young MR. Increased aberrance of cytokine expression in plasma of patients with more advanced squamous cell carcinoma of the head and neck. *Cytokine* 2004;25:220–8.
- [8] Weiss R, Scheibelhofer S, Gabler M, Ferreira F, Leitner WW, Thalhamer J. Is genetic vaccination against allergy possible? *Int Arch Allergy Immunol* 2006;139:332–45.
- [9] Elhini A, Abdelwahab S, Ikeda K. Th1 and Th2 cell population in chronic ethmoidal rhinosinusitis: a chemokine receptor assay. *Laryngoscope* 2005;115:1272–7.
- [10] Kamil A, Ghaffar O, Lavigne F, Taha R, Renzi PM, Hamid Q. Comparison of inflammatory cell profile and Th2 cytokine expression in the ethmoid sinuses, maxillary sinuses, and turbinates of atopic subjects with chronic sinusitis. *Otolaryngol Head Neck Surg* 1998;118:804–9.
- [11] Bernstein JM, Ballou M, Rich G, Allen C, Swanson M, Dmochowski J. Lymphocyte subpopulations and cytokines in nasal polyps: is there a local immune system in the nasal polyp? *Otolaryngol Head Neck Surg* 2004;130:526–35.
- [12] Lal D, Baroody FM, Weitzel EK, deTineo M, Naclerio RM. Total IgE levels do not change 1 year after endoscopic sinus surgery in patients with chronic rhinosinusitis. *Int Arch Allergy Immunol* 2006;139:146–8.
- [13] Riccio AM, Tosca MA, Cosentino C, Pallestrini E, Ameli F, Canonica GW, et al. Cytokine pattern in allergic and non-allergic chronic rhinosinusitis in asthmatic children. *Clin Exp Allergy* 2002;32:422–6.
- [14] Tosca MA, Cosentino C, Pallestrini E, Caligo G, Milanese M, Ciprandi G. Improvement of clinical and immunopathologic parameters in asthmatic children treated for concomitant chronic rhinosinusitis. *Ann Allergy Asthma Immunol* 2003;91:71–8.
- [15] Bryson JM, Tasca RA, Rowe-Jones JM. Local and systemic eosinophilia in patients undergoing endoscopic sinus surgery for chronic rhinosinusitis with and without polyposis. *Clin Otolaryngol Allied Sci* 2003;28:55–8.
- [16] Zachariae H. Prevalence of joint disease in patients with psoriasis: implications for therapy. *Am J Clin Dermatol* 2003;4:441–7.
- [17] Matei I, Matei L. Cytokine patterns and pathogenicity in autoimmune diseases. *Rom J Intern Med* 2002;40:27–41.
- [18] Ghoreschi K, Rocken M. Immune deviation strategies in the therapy of psoriasis. *Curr Drug Targets Inflamm Allergy* 2004;3:193–8.
- [19] Book DT, Smith TL, McNamar JP, Saeian K, Binion DG, Toohill RJ. Chronic sinonasal disease in patients with inflammatory bowel disease. *Am J Rhinol* 2003;17:87–90.
- [20] Bartholo RM, Zaltman C, Elia C, Cardoso AP, Flores V, Lago P, et al. Bronchial hyperresponsiveness and analysis of induced sputum cells in Crohn's disease. *Braz J Med Biol Res* 2005;38:197–203.
- [21] Keating GM, Perry CM. Infliximab: an updated review of its use in Crohn's disease and rheumatoid arthritis. *BioDrugs* 2002;16:111–48.
- [22] Hayakawa H, Sato A, Imokawa S, Toyoshima M, Chida K, Iwata M, et al. Bronchiolar disease in rheumatoid arthritis. *Am J Respir Crit Care Med* 1996;154:1531–6.
- [23] Alobid I, Guilemany JM, Mullol J. Nasal manifestations of systemic illnesses. *Curr Allergy Asthma Rep* 2004;4:208–16.
- [24] Jones RL, Crowe P, Chavda SV, Pahor AL. The incidence of sinusitis in patients with multiple sclerosis. *Rhinology* 1997; 35:118–9.
- [25] Gay D, Dick G, Upton G. Multiple sclerosis associated with sinusitis: case-controlled study in general practice. *Lancet* 1986;1:815–9.
- [26] Wang X, Kim J, McWilliams R, Cutting GR. Increased prevalence of chronic rhinosinusitis in carriers of a cystic fibrosis mutation. *Arch Otolaryngol Head Neck Surg* 2005; 131:237–40.
- [27] Genovese MC. Biologic therapies in clinical development for the treatment of rheumatoid arthritis. *J Clin Rheumatol* 2005;11(3 Suppl):S45–S54.

Copyright of *Acta Oto-Laryngologica* is the property of Taylor & Francis Ltd and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.