

# Superantigens and Chronic Rhinosinusitis: Detection of Staphylococcal Exotoxins in Nasal Polyps

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**Objective/Hypothesis:** The role of infectious agents in the etiology of chronic rhinosinusitis with nasal polyposis (CRSwNP) remains unclear. Recent studies have provided indirect evidence of exposure to staphylococcal exotoxins in the blood and polyp tissue of patients with CRSwNP. These exotoxins have the capacity to act as superantigens, bypassing normal antigen processing and directly stimulating a massive inflammatory response. The objective of the study was to analyze mucus and polyp tissue samples from patients with CRSwNP for the presence of staphylococcal exotoxins. **Study Design:** Prospective study. **Methods:** Tissue and mucus samples were obtained from 42 patients undergoing endoscopic sinus surgery for chronic rhinosinusitis and 11 normal control patients. Twenty-nine of 42 patients had chronic rhinosinusitis with bilateral nasal polyposis, 2 had antrochoanal polyps, and 11 had chronic rhinosinusitis without nasal polyps. Eleven patients without chronic rhinosinusitis or polyps served as normal control patients. Specimens were analyzed for the presence of five staphylococcal exotoxins (SEA, SEB, SEC, SED, and toxic shock syndrome toxin type 1 [TSST-1]) using enzyme-linked immunosorbent assay (ELISA). Histological analysis of specimens and mean eosinophil counts were correlated with the presence of toxin. **Results:** At least one toxin was detected in 14 of 29 patients with bilateral nasal polyposis. Nine of the 14 patients also had positive findings for additional toxins. The dominant histological pattern in the CRSwNP patient group was polypoid mucosa

with edema, which was found in both ELISA-positive and ELISA-negative patients. Mean eosinophil counts tended to be higher in ELISA-positive patients with polyps compared with patients without toxin detection. No toxin was detected in the 11 specimens taken from normal control patients. Only 1 of the 13 patients with CRS without polyps had positive ELISA results for toxin. **Conclusion:** The current study demonstrates the presence of superantigen toxins in 14 of 29 patients with CRSwNP, with SEB and TSST-1 being the most common. Further studies are necessary to correlate the presence of toxin with the pathological changes present in polyp tissue. **Key Words:** Chronic rhinosinusitis, nasal polyps, superantigens, eosinophil, ELISA.

*Laryngoscope*, 115:1580–1585, 2005

## INTRODUCTION

Chronic rhinosinusitis (CRS) is one of the most common health care problems in the United States, affecting almost 15% of the population.<sup>1</sup> The Sinus and Allergy Health Partnership defined CRS as a group of disorders characterized by inflammation of the mucosa of the nose and paranasal sinuses of at least 12 consecutive weeks' duration.<sup>1</sup> This definition is purposely broad, encompassing a wide range of clinical entities presenting with a similar symptom complex. Approximately 20% of patients with CRS exhibit bilateral nasal polyposis (NP), representing a group that is particularly refractory to both medical and surgical (endoscopic sinus surgery) intervention.<sup>3</sup> Furthermore, histological analysis of polyp specimens reveals tissue eosinophilia and edema in the vast majority of cases, suggesting that chronic rhinosinusitis with nasal polyposis (CRSwNP) represents a distinct subset of CRS with a more narrow range of causes.<sup>1,2</sup> Recent evidence has suggested that exotoxins secreted by colonizing *Staphylococcus aureus* are capable of triggering the inflammatory infiltrate characteristic of CRSwNP through their potential to generate a "superantigen response."<sup>3</sup>

Superantigens are powerful T-cell mitogens, which are active at concentrations as low as 0.1 pg/mL, that are

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Editor's Note: This Manuscript was accepted for publication April 20, 2005.

Supported by the Ernest S. Bazley Grant to Northwestern Memorial Hospital and Northwestern University Feinberg School of Medicine.

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DOI: 10.1097/01.mlg.0000168111.11802.9c

capable of subverting a normal acquired immune response.<sup>4</sup> Superantigens have the ability to activate up to 30% of the T-cell population in contrast to the conventional antigen response, which activates only 0.01% of all T cells. Superantigens bypass normal antigen processing within antigen-presenting cells, binding directly to a region outside the peptide-binding groove of the major histocompatibility complex (MHC) Class II molecule. Superantigens also bind to the V $\beta$  region of the T-cell receptor, thereby bridging the MHC Class II molecule on the antigen-presenting cell and the T-cell receptor, resulting in massive proliferation and activation of the targeted T-cells. Superantigens have been implicated in the pathogenesis of diseases such as atopic dermatitis and asthma, which have histopathological changes that are similar to CRSwNP.<sup>5,6</sup> Furthermore, the observed pattern of cytokine release with superantigen stimulation (interleukins 4, 5, and 13 [IL-4, IL-5, and IL-13] and others) should theoretically be capable of generating the severe eosinophilia and lymphocytic infiltration seen in CRSwNP.<sup>3,7</sup>

*Staphylococcus aureus* can secrete at least 19 different exotoxins capable of functioning as superantigens.<sup>8</sup> This organism has been cultured from the upper airways of a high percentage of patients with CRSwNP.<sup>3</sup> Evidence for superantigens as disease modifiers in CRSwNP was first described in 2001 by Bachert et al.,<sup>9</sup> who demonstrated specific immunoglobulin E (IgE) to staphylococcal toxins (SEA, SEB) in polyp tissues of 50% of patients with CRSwNP. Staphylococcal toxin-specific IgE was also identified in the serum of a high percentage of patients with CRSwNP; whether or not this was related to the concomitant presence of asthma was unclear.<sup>10,11</sup> Nasal cultures obtained from patients with CRSwNP have also revealed a high incidence of toxin-secreting *S. aureus* strains.<sup>12</sup> Although the cultured bacteria secreted superantigenic toxins in vitro, whether these exotoxins would also be secreted in vivo was not clear. Flow cytometric studies on the lymphocyte population derived from polyps demonstrated clonal expansion of specific T-cell V $\beta$  motifs, which is the hallmark of a superantigen response.<sup>12–14</sup>

Currently, only indirect evidence exists regarding the role of superantigens in the pathogenesis and disease maintenance of CRSwNP. In general, these earlier studies have demonstrated a host response indicative of superantigen exposure. The present study used an enzyme-linked immunosorbent assay (ELISA) (Toxin Technology, Sarasota, FL) to detect the common staphylococcal exotoxins SEA, SEB, SEC1–SEC3, SED, and toxic shock syndrome toxin type 1 (TSST-1) in the polyp tissue and mucus of patients with CRSwNP. The goal of the present study was to test whether there is direct evidence for the presence of staphylococcal superantigenic toxins in CRSwNP.

## PATIENTS AND METHODS

Following approval by the Northwestern University Medical School Institutional Review Board committee, 42 patients undergoing endoscopic sinus surgery and 11 normal control patients were recruited, with informed consent obtained for all patients included in the study. Patients undergoing endoscopic sinus surgery met the criteria for CRS as defined by the Sinus and Allergy Health Partnership.<sup>2</sup> The presence of bilateral nasal

polyps was confirmed by office endoscopy and computed tomography (CT) imaging. All patients scheduled for surgery failed adequate trials of conservative medical therapy (prolonged antibiotic regimens, nasal steroid sprays, oral steroids, saline irrigations, and decongestants) for control of symptoms. Sinonasal mucus and polyp tissue samples were collected at the time of surgery from the CRS group. Samples from the control group were collected in the office setting. Polyp and mucus specimens were processed for toxin detection (SEA, SEB, SEC, SED, and TSST-1) using an ELISA technique. In addition, surgical tissue specimens were embedded in paraffin, sectioned into 5- $\mu$ m slices, and placed on glass slides for routine pathological examination and hematoxylin and eosin (H&E) staining.

## ELISA Procedure

Each plate was coated with 100  $\mu$ L of a 10- $\mu$ g/mL solution of purified anti-SET (SEA, SEB, SEC, SED, SEE) or anti-TSST-1 rabbit immunoglobulin G (IgG) in a coating buffer of 0.01 mol/L sodium carbonate, pH 9.6. The plate was placed in a humid chamber on a shaker for 12 to 18 hours at 37°C. The plate was washed three times with phosphate-buffered saline (PBS) containing 0.05% Tween-20 (PBS-Tween). On the fourth wash, the PBS-Tween was allowed to sit for 15 minutes, then discarded. Standard solutions of SET and TSST-1 were made using PBS-Tween. Six serial dilutions of the toxin standards ranging from 10 ng/mL to 0.32 ng/mL were generated as standards. A buffer blank or negative control was assayed to account for any nonspecific color reactions. All control and test samples were run in triplicate. The plates were incubated on a shaker for 2 hours at 37°C. The plates were then washed three times with PBS-Tween. After washing, 100  $\mu$ L of the conjugate (antitoxin) was added to each well and incubated for 1 hour while shaking at 37°C. The plate was then washed five times with PBS-Tween. After the final wash step, 100  $\mu$ L of the substrate solution was added to each well. Fifteen minutes was allotted for the color to develop. The reaction was then stopped with 25  $\mu$ L of a 5% sodium dodecyl-sulfate solution. The absorbance was read on a plate reader at 405 nm. Samples with a higher absorbance than the 0.32-ng/mL standard, which were significantly higher (>50%) than the blanks, were considered positive for that toxin. Each plate was tested against three positive control samples run at 1.25 ng/mL, 0.63 ng/mL, and 0.32 ng/mL, respectively, and one negative control sample. The negative control sample (0 ng/mL) was made of 0.05% PBS-Tween. The ELISA kit that was used is commercialized for the detection of the previously named staphylococcal toxins in culture supernatants and test extracts with a sensitivity limit of 31 pg/mL.

## Microscopic Analysis

Surgical specimens were examined using a standard microscope by one senior pathologist who was blinded to clinical data. Sections were examined initially under low-powered view for the areas with the highest eosinophil counts. Then, eosinophil counts were obtained using an optical rectangle under high-powered view (original magnification  $\times 400$ ) from three distinct areas corresponding to those with the highest eosinophil infiltration. A stage graticule was used to calculate the area of the field of view at original magnification  $\times 400$ . The area of counted eosinophils corresponded to a 0.16  $\times$  0.12-mm rectangle with a field diameter of 0.21 mm.

Surgical specimens were also evaluated for histological changes seen in CRS and CRSwNP on H&E sections. Using established methodology, changes were grouped into three distinct histopathological patterns: polypoid mucosa with edema (PME), glandular hyperplasia (GH), and a mixture of the two.<sup>19</sup> Although some elements of both patterns were seen in all cases,

TABLE I.  
Clinical Characteristics and ELISA Results.

| Patient No.               | Age (y) | Gender | Allergies | Asthma | Specimen    | Toxin Detected       | Pathological Finding(s) | Eosinophil Count No./HPF | Histological Finding(s) |
|---------------------------|---------|--------|-----------|--------|-------------|----------------------|-------------------------|--------------------------|-------------------------|
| <b>CRSsNP Group</b>       |         |        |           |        |             |                      |                         |                          |                         |
| 1                         | 48      | F      | Yes       | No     | Polyp       | Neg                  | Polyps                  | 37                       | Mixed (PME>GH)          |
| 2                         | 61      | M      | No        | No     | Polyp       | SEB, SED             | Polyps                  | 4                        | PME                     |
| 3                         | 49      | F      | No        | No     | Polyp       | SEB                  | Polyps                  | 28                       | PME                     |
| 4                         | B       | F      | Yes       | Yes    | Polyp       | SEB                  | Polyps                  | 143                      | PME                     |
| 5                         | 56      | F      | No        | No     | Mucus       | Neg                  | Polyps                  | 5                        | Fibrotic                |
| 6                         | 34      | M      | Yes       | No     | Polyp/mucus | SEA, SEB             | Polyps                  | 107                      | PME                     |
| 7                         | 35      | M      | Yes       | No     | Polyp/mucus | SEB, SED             | Polyps                  | 52                       | Mixed (PME>GH)          |
| 8                         | 24      | M      | No        | No     | Mucus       | Neg                  | Polyps                  | 154                      | PME                     |
| 9                         | 26      | F      | No        | No     | Polyp       | Neg                  | Polyps                  | 18                       | GH                      |
| 10                        | 31      | F      | Yes       | Yes    | Mucus       | SEB                  | Polyps                  | 134                      | PME                     |
| 11                        | 36      | F      | Yes       | Yes    | Polyp       | Neg                  | Polyps                  | 41                       | Mixed (PME>GH)          |
| 12                        | 53      | F      | Yes       | Yes    | Mucus       | Neg                  | Polyps                  | 106                      | PME                     |
| 13                        | 26      | F      | Yes       | No     | Mucus       | SEB, TSST-1          | Polyps                  | 98                       | Mixed (PME>GH)          |
| 14                        | 71      | M      | Yes       | Yes    | Mucus       | SEA, SEB             | Polyps                  | 27                       | PME                     |
| 15                        | 64      | M      | Yes       | Yes    | Mucus       | Neg                  | Polyps                  | No slide                 | No slide                |
| 16                        | 51      | F      | Yes       | Yes    | Polyp       | Neg                  | Polyps                  | 85                       | Mixed (GH>PME)          |
| 17                        | 26      | M      | Yes       | Yes    | Polyp       | Neg                  | Polyps                  | 128                      | Mixed (GH>PME)          |
| 18                        | 72      | F      | No        | Yes    | Mucus       | Neg                  | Polyps                  | 87                       | PME                     |
| 19                        | 40      | F      | Yes       | Yes    | Polyp       | Neg                  | Polyps                  | 7                        | GH                      |
| 20                        | 31      | M      | No        | No     | Polyp       | Neg                  | Polyps                  | 25                       | PME                     |
| 21                        | 64      | M      | No        | No     | Mucus       | Neg                  | Polyps/IP               | 76                       | PME                     |
| 22                        | 60      | M      | No        | No     | Polyp       | TSST-1               | Polyps                  | 2.3                      | PME                     |
| 23                        | 61      | M      | No        | No     | Polyp/mucus | SEA, SEB/SEA, TSST-1 | Polyps                  | 157                      | PME                     |
| 24                        | 39      | F      | No        | No     | Polyp/mucus | TSST-1/SEA, TSST-1   | Polyps                  | 81                       | PME                     |
| 25                        | 36      | F      | Yes       | Yes    | Polyp       | SEB                  | Polyps                  | 99.7                     | PME                     |
| 26                        | 26      | F      | Yes       | No     | Mucus       | TSST-1               | Polyps                  | 110                      | PME                     |
| 27                        | 37      | F      | No        | No     | Polyp/mucus | Neg                  | Polyps                  | 0                        | PME                     |
| 28                        | 53      | M      | Yes       | No     | Polyp       | SEA, TSST-1          | Polyps                  | 26.7                     | PME                     |
| 29                        | 55      | F      | Yes       | No     | Polyp/mucus | Neg                  | Polyps                  | 81                       | PME                     |
| <b>Nonpolyp CRS Group</b> |         |        |           |        |             |                      |                         |                          |                         |
| 30                        | 25      | M      | No        | No     | Polyp       | Neg                  | ACP                     | 2                        | Mixed (PME>GH)          |
| 31                        | 30      | M      | No        | No     | Polyp       | Neg                  | ACP                     | 2                        | PME                     |
| 32                        | 46      | M      | No        | No     | Mucus       | Neg                  | CRS, nonpolyp           | 0.3                      | GH                      |
| 33                        | 58      | M      | No        | No     | Mucus       | Neg                  | CRS, nonpolyp           | 0.7                      | Mixed (GH>PME)          |
| 34                        | 57      | F      | No        | No     | Mucus       | Neg                  | CRS, nonpolyp           | 8.7                      | PME                     |
| 35                        | 52      | M      | Yes       | No     | Mucus       | Neg                  | CRS, nonpolyp           | 0                        | Normal                  |
| 36                        | 52      | F      | Yes       | No     | Mucus       | Neg                  | CRS, nonpolyp           | 0                        | GH                      |
| 37                        | 52      | F      | Yes       | No     | Mucus       | Neg                  | CRS, nonpolyp           | 2.7                      | Mixed (GH>PME)          |
| 38                        | 59      | M      | Yes       | No     | Mucus       | SEA, SEB, TSST-1     | CRS, nonpolyp           | 1                        | Mixed (PME>GH)          |
| 39                        | 41      | F      | No        | No     | Mucus       | Neg                  | CRS, nonpolyp           | 0                        | Mixed (GH>PME)          |
| 40                        | 31      | M      | No        | No     | Mucus       | Neg                  | CRS, nonpolyp           | 2                        | GH                      |
| 41                        | 33      | F      | Yes       | Yes    | Mucus       | Neg                  | CRS, nonpolyp           | 29.7                     | PME                     |
| 42                        | 55      | F      | No        | No     | Mucus       | Neg                  | CRS, nonpolyp           | No slide                 | No slide                |

TABLE I.  
Continued.

| Patient No.          | Age (y) | Gender | Allergies | Asthma | Specimen | Toxin Detected | Pathological Finding(s) | Eosinophil Count | Histological Finding(s) |
|----------------------|---------|--------|-----------|--------|----------|----------------|-------------------------|------------------|-------------------------|
| <b>Control Group</b> |         |        |           |        |          |                |                         |                  |                         |
| 43                   | 30      | F      | No        | No     | Mucus    | Neg            | Control                 | n/a              | n/a                     |
| 44                   | 47      | M      | Yes       | No     | Mucus    | Neg            | Control                 | n/a              | n/a                     |
| 45                   | 45      | M      | No        | No     | Mucus    | Neg            | Control                 | n/a              | n/a                     |
| 46                   | 48      | F      | No        | No     | Mucus    | Neg            | Control                 | n/a              | n/a                     |
| 47                   | 51      | F      | No        | No     | Mucus    | Neg            | Control                 | n/a              | n/a                     |
| 48                   | 30      | F      | Yes       | No     | Mucus    | Neg            | Control                 | n/a              | n/a                     |
| 49                   | 37      | M      | Yes       | No     | Mucus    | Neg            | Control                 | n/a              | n/a                     |
| 50                   | 43      | M      | Yes       | No     | Mucus    | Neg            | Control                 | n/a              | n/a                     |
| 51                   | 34      | M      | Yes       | No     | Mucus    | Neg            | Control                 | n/a              | n/a                     |
| 52                   | 34      | F      | No        | No     | Mucus    | Neg            | Control                 | n/a              | n/a                     |
| 53                   | 57      | F      | No        | No     | Mucus    | Neg            | Control                 | n/a              | n/a                     |

CRSwNP, chronic rhinosinusitis with nasal polyposis; Neg, negative; PME, polypoid mucosa with edema; GH, glandular hyperplasia; TSST-1, toxic shock syndrome toxin type 1; CRS, chronic rhinosinusitis; ACP = antrochoanal polyp; SEB, staphylococcal exotoxin; n/a, not applicable; HPF, high powered field.

specimens with an obvious predominance of PME or GH were labeled as such. When both elements were commonly present on the slide, specimens were labeled as mixed, with the predominant feature noted (PME>GH or GH>PME).

## RESULTS

Fifty-three patients (29 female and 24 male patients) participated in the present study. The patients were divided into three groups: patients with CRSwNP (CRSwNP group) (n = 29), patients with CRS without polyps (nonpolyp CRS group) (n = 13), and the control group (n = 11). The CRSwNP group consisted of 29 patients with bilateral NP diagnosed by nasal endoscopy. The nonpolyp CRS group consisted of 11 patients with nonpolyp CRS and 2 patients with antrochoanal polyps. The control group consisted of 11 patients without signs or symptoms of CRS. The average ages of the patients in the CRSwNP and nonpolyp CRS groups were 45.2 and 45.5 years, respectively. Thirty-eight percent (11 of 29) of the patients in the CRSwNP group had asthma and 59% (17 of 29) had atopy (Table I). In the nonpolyp CRS group, 38% of the patients (5 of 13) had atopy and 1 patient had asthma.

### Enzyme-Linked Immunosorbent Assay Results

Samples from 29 patients with CRSwNP, 11 control patients, and 13 patients with CRS without polyps were processed for toxin detection by the ELISA technique. Samples from 15 patients were positive for toxin on the ELISA testing, which consisted of 14 patients with CRSwNP and 1 patient with nonpolyp CRS. In addition, 9 of those 15 patients were positive for more than one toxin. In the CRSwNP group (n = 21) there were 12 polyp and 19 mucus specimens tested for the presence of toxin with the ELISA kit. Ten of 20 polyp samples (50%) and 8 of 27 mucus samples (30%) were found to be positive for toxin. There were no positive results in the control group (n = 11) (Table I). Using the  $\chi^2$  test, our results showed a statistically significant association between toxin detection and patients with CRSwNP ( $P < .002$ ). There was no significant difference between the control and the nonpolyp CRS groups ( $P > .05$ ).

### Eosinophils and Histological Findings

The mean eosinophil count was significantly higher ( $P > .001$ ) in the CRSwNP group compared with the nonpolyp CRS group (68.6 versus 4.1). In comparing the degree of eosinophilic infiltration in polyp tissue between patients with positive (n = 14) and negative ELISA (n = 15) results within the CRSwNP group, we found the mean eosinophil counts to be 72 and 61, respectively. There was a trend toward higher eosinophil levels in the patients who tested positive for toxins, although this was not statistically significant ( $P = .33$ ). In reviewing the histological findings between the ELISA-positive and ELISA-negative patients within the CRSwNP group, we found no correlation between histological appearance and the presence of toxin. The dominant histological pattern in the CRSwNP group was PME, which was found in both ELISA-positive and ELISA-negative patients. In the polyp group, histologically, 19 samples were categorized as polypoid in appearance (PME), 4 as mixed (PME>GH), 2 as

mixed (GH>PME), and 2 as GH, and there were 2 samples with unclassified changes. In specimens with positive ELISA results, 12 were classified as PME and 2 as mixed (PME>GH).

## DISCUSSION

The “superantigen hypothesis” proposes that staphylococcal exotoxins promote the development of the lymphocytic and eosinophilic mucosal infiltrate associated with the presence of bilateral nasal polyposis.<sup>3</sup> In polyp tissue, studies have demonstrated both specific IgE against staphylococcal toxins and clonal expansion of polyp T cells expressing specific V $\beta$  motifs<sup>9,14</sup>. Taken together, the studies demonstrate evidence of both a conventional and a superantigenic host response to staphylococcal exotoxins in CRSwNP, indirectly suggesting mucosal exposure. In the current study, “direct” evidence for the presence of staphylococcal superantigens has been demonstrated in the nasal cavity of 14 of 29 patients with CRSwNP with the use of ELISA. Toxin was demonstrated in only 1 of the 13 patients in the nonpolyp CRS group and in none of the 11 normal control patients.

*Staphylococcus aureus* has been cultured from the nasal cavity of more than 75% of patients with CRSwNP but of only 25% of the general population. A large percentage of strains of *S. aureus* produce superantigenic toxins, at least in vitro.<sup>12</sup> Polyp tissue analysis has supported a superantigen effect in approximately 50% of cases of CRSwNP using multiple techniques.<sup>9,11,12</sup> In the current study of CRSwNP, we detected toxin in 48% of the polyp patients (14 of 29 patients) and in 7.7% of the nonpolyp CRS patients (1 of 13 patients), with 9 of the 15 positive patients demonstrating more than one toxin. The ELISA technique used in the study was designed to detect the seven most common staphylococcal toxins (SEA, SEB, SEC1–SEC3, SED, and TSST-1). The incidence of exposure is likely to be higher because the present study only tested for the presence of 7 of the 19 known staphylococcal superantigens. Furthermore, the detection limits of the ELISA kit used in the present study range from 1.25 to 0.32 ng/mL.

Histological analysis of polyp tissue in the ELISA-positive and ELISA-negative groups failed to reveal any significant differences. However, a trend toward higher eosinophil counts in the ELISA-positive group was detected. In addition, the present study assessed only intact eosinophils, possibly underestimating the total number in the polyp tissue. Future studies analyzing both activated and degranulated eosinophils may show a more significant association with the presence of toxins.

The current study provides additional data in support of the *superantigen hypothesis* of CRSwNP. Although evidence continues to mount supporting staphylococcal superantigens as disease modifiers in CRSwNP, the precise role of toxins in polyp formation remains uncertain. Specifically, the sinonasal tract is a site of interface with the external environment wherein foreign antigens are encountered and typically cleared.<sup>17</sup> Superantigens, which have the ability to bypass normal antigen processing, would be capable of directly stimulating lymphocytes already present in the mucosa. Histopathologically, the T

helper-cell type 1/T helper-cell type 2 profile characteristic of CRSwNP should, at least theoretically, be observed. Moreover, the importance of T helper-cell type 2 immunity across mucosal barriers in general heightens the potential for a strong eosinophilic tissue response subsequent to intranasal superantigen challenge.<sup>18</sup> Nevertheless, the relatively ubiquitous nature of toxin-secreting *S. aureus* indirectly suggests that only a minor percentage of patients exposed to these exotoxins in the nose will develop CRSwNP. Other as yet unknown genetic and/or environmental factors are probably necessary to generate the clinical disease. In apparent conflict with the superantigen hypothesis, it has been suggested that fungi, which are present as a normal contaminant of nasal mucus, may trigger a hypersensitivity response mediating the formation of nasal polyps. From this perspective, CRSwNP could be viewed as being analogous to inflammatory bowel disease wherein the tolerance mechanisms toward commensal organisms are impaired.<sup>19</sup> Given the ubiquitous nature of fungi, this hypothesis would also require additional environmental or genetic factors in addition to fungal antigens for disease to manifest. Therefore, the two hypotheses are not in direct conflict, and further work is necessary to define the role of either agent in CRSwNP.

## CONCLUSION

The present study provides direct evidence for the presence of superantigens in the nasal cavity of patients with CRSwNP. Our research is consistent with the possibility of superantigens as etiological agents in the development of bilateral nasal polyposis.

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