Am J Otolaryngol 39 (2018) 293–298

Contents lists available at ScienceDirect

Am J Otolaryngol

journal homepage: www.elsevier.com/locate/amjoto

Cortactin expression in nasal polyps of Aspirin-Exacerbated Respiratory Disease (AERD) patients

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ARTICLE INFO

Keywords:
Cortactin
Aspirin-exacerbated respiratory disease
AERD
Nasal polyps
Asthma
Allergy

ABSTRACT

Purpose: The term aspirin-exacerbated respiratory disease (AERD) refers to a combination of asthma, chronic rhinosinusitis with nasal polyposis (CRSwNP), and acute respiratory tract reactions to nonsteroidal anti-inflammatory drugs. AERD has now been included among the CRSwNP endotypes, and is considered one of the most aggressive in terms of disease recurrence.

Cortactin is a multi-domain protein with a part in several cellular mechanisms involving actin assembly and cytoskeleton arrangement. Cortactin seems to have a role in inflammatory responses and to be implicated in human airway secretion and contraction mechanisms.

The novel aim of the present study was to examine cortactin expression in nasal polyps of a consecutive cohort of AERD patients and in nasal mucosa of a control group of patients.

Materials and methods: Cortactin expression was assessed immunohistochemically in nasal polyps from 18 consecutive AERD patients who underwent endoscopic sinus surgery and in nasal mucosa of 19 patients without chronic rhinosinusitis.

Results: Concomitant allergy was found in 11 AERD patients, most of them male (8 cases; $p = 0.02$). Cortactin expression in nasal polyps was definitely high (+3) in 17 out of 18 cases, in both epithelial cells (cytoplasmic and membranous immunoreactivity) and activated fibroblasts. A higher cortactin expression was seen in female than in male AERD patients ($p = 0.05$).

Conclusions: Given this preliminary evidence of cortactin upregulation in the polyps of AERD patients, prospective studies could further investigate the role of cortactin in the biology of AERD, and the potential role of cortactin-targeted approaches in integrated AERD treatments.

1. Introduction

The term aspirin-exacerbated respiratory disease (AERD) refers to a combination of asthma, chronic rhinosinusitis with nasal polyposis (CRSwNP), especially the eosinophilic histotype, and acute upper and/or lower respiratory tract reactions to the ingestion of nonsteroidal anti-inflammatory drugs (NSAIDs) [1]. Additional features can include blood hypereosinophilia, abdominal and dermatological disorders, and intolerance of alcoholic beverages [2]. AERD affects from 0.3% to 0.9% of the general population, usually developing in the third and fourth decades of life [3]. It has now been included among the CRSwNP endotypes, and is one of the most aggressive in terms of disease recurrence [1].

Cortactin is a multi-domain protein that takes part in several cellular mechanisms involving actin assembly and cytoskeleton arrangement [4,5]. The locus of cortactin CTTN is in the 11q13 chromosomal region. It is a gene frequently amplified in several types of human cancer (adenocarcinoma of the breast and colon, squamous cell carcinoma of the esophagus or head and neck) [6,7]. Cortactin overexpression has consequently been associated with a tumor's aggressiveness, invasiveness, and metastatic potential, and with a poor prognosis [8–10].

Several studies [11–15] have recently investigated the role of cortactin in non-neoplastic diseases, and particularly in inflammatory disorders involving smooth muscle contraction and mucus secretion in the human airways.

Given the emerging role of cortactin in regulating inflammatory responses, and its implication in human airway secretion and contraction mechanisms, the novel, main aim of the present study was to examine cortactin expression in nasal polyps from a consecutive cohort of

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https://doi.org/10.1016/j.amjoto.2018.03.012
Received 22 January 2018

AERD patients, who were stratified by their demographic, clinical, laboratory, and prognostic features; cortactin immunostaining was determined also in normal nasal mucosa from a control group of patients without chronic rhinosinusitis. A second endpoint of the study was to assay blood basophils, eosinophils, and calculate the neutrophils-to-lymphocytes ratio (NLR) in the same cohort of patients.

2. Methods

2.1. Patients

This retrospective study was approved by our Otolaryngology Section's in-house committee and conducted according to the principles of the Helsinki Declaration. All patients and controls signed a detailed informed consent form regarding the processing and publication of their data and images.

The study was performed on a consecutive cohort of Caucasian adult patients (≥18 years) with a diagnosis of AERD. Asthma was diagnosed clinically and confirmed by spirometry and methacholine challenge tests. Hypersensitivity to aspirin and other cyclooxygenase-1 (COX-1) inhibiting NSAIDs was documented on the grounds of patients' clinical history. Rigid 0° and 30° (Ø 4 mm) endoscopes, and CT scans of the paranasal sinuses were used to detect and classify CRSwNP, as well as for follow-up purposes. Patients with endoscopic evidence of polyps grades 2 or 3 according to Mackay and Lund [16] and failing to respond to topical and oral steroid therapy given for three consecutive months as recommended in the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) guidelines [17] underwent endoscopic sinus surgery (ESS).

The following were reasons for exclusion: pregnancy, autoimmune disease, acute or chronic infectious diseases other than sinusitis, malignancies, hematological disorders, or chronic renal insufficiency.

All patients underwent preoperative laboratory tests at least 3 months after withdrawing oral steroids, and at least 1 month after stopping nasal steroid treatments. In particular, a blood sample was taken to obtain neutrophil, lymphocyte, eosinophil, and basophil counts, and the NLR was calculated [18]. All assays were performed at the same laboratory (EIA Unit, Laboratory Medicine Service, Padova General Hospital; certified in accordance with ISO 15189).

For the histopathological examination, surgical specimens were stained with hematoxylin and eosin, and 3 high-power fields (HPF) (magnification 400×) from each specimen were examined by a pathologist (FM) to quantify the eosinophil component. As previously reported [19], CRSwNP was classified as eosinophilic (≥10 eosinophils/HPF) or non-eosinophilic (< 10 eosinophils/HPF).

After surgery, all patients performed nasal irrigations with isotonic saline solution twice daily and applied the same topical nasal steroids as they had used preoperatively, in accordance with the EPOS guidelines [17]. During periods of pollination, patients with a known pollen allergy were treated with antihistamines.

Follow-up endoscopies were scheduled 3, 6, and 12 months after ESS, and yearly thereafter. Patients with endoscopic evidence of at least grade 1 polyposis [16] were classified as cases of recurrence.

2.2. Immunohistochemistry

Immunohistochemical reactions were conducted on sections 4–5 μm thick obtained from formalin-fixed and paraffin-embedded samples from 18 patients with AERD and 19 patients without chronic rhinosinusitis that underwent nasal biopsy and resulted completely normal at histological examination. All immunohistochemical stains were performed with a fully automated system (BondmaX Leica Microsystems, Wetzlar, Germany), using the Bond Polymer Refine Detection kit (Leica Microsystems, Wetzlar, Germany), and a rabbit anti-cortactin antibody (monoclonal EP1922Y; Abcam, Cambridge, UK; working dilution 1:200, 30 min, citrate buffer), according to the manufacturer's instructions. The prepared sections were lightly counterstained with hematoxylin. Appropriate positive controls, and sections incubated without any primary antibody as negative controls were run concurrently according to the manufacturer's recommendations. For each slide, cortactin immunostaining was scored by a pathologist (LN). In AERD patients' specimens, cytoplasmic cortactin expression was measured as the percentage of positive cells and scored as: 0 = < 1%; +1: 1–25%; +2: 26–65% and +3: > 66%. Staining intensity was graded as: 0 = none; +1: weak; +2: moderate; +3 = strong. An overall H-score was calculated as: (1 + intensity) / (3 × expression score) [20].

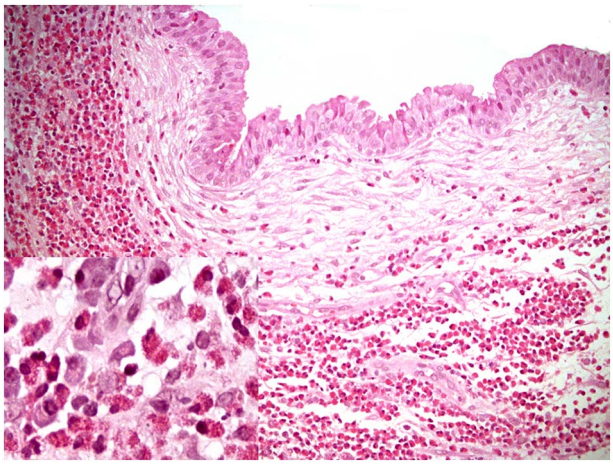

Fig. 1. Representative case of eosinophilic polyp mucosa showing high eosinophil density (box on left; hematoxylin and eosin, magnification 200×).

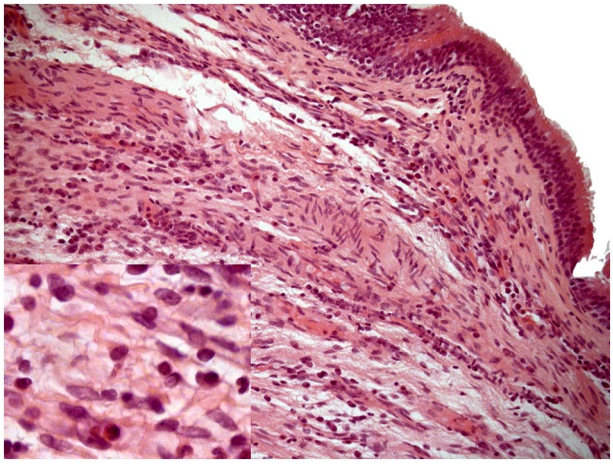

Fig. 2. Representative case of non-eosinophilic polyp mucosa (box on left; hematoxylin and eosin, magnification 200×).

2.3. Statistical analysis

Because of the small sizes of the sub-cohorts considered, the statistical significance of any differences between means was ascertained using a non-parametric test (the Mann–Whitney test) to compare between-group findings. Fisher's exact test and Spearman's rank correlation test were also used, as appropriate. A p value < 0.05 was considered significant, while values in the range of $0.08 \geq p \geq 0.05$ were considered as indicating a statistical trend. The STATA 8 statistical package (Stata Corp LP, College Station, Texas) was used for all analyses.

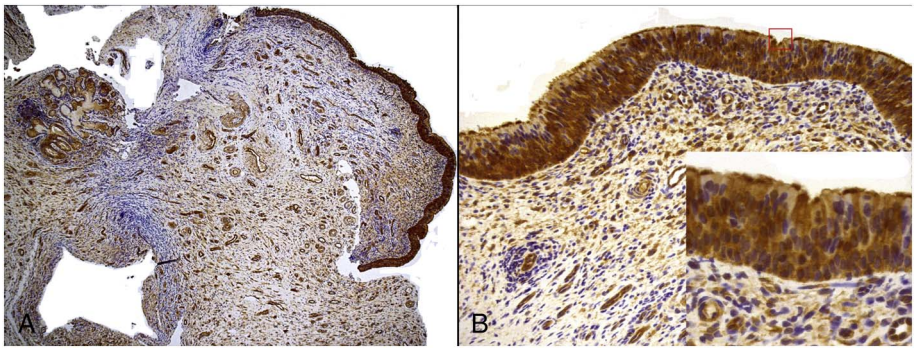

Fig. 3. Representative case of eosinophilic polyp showing strong staining for cortactin (A; magnification 25×); high magnification shows exclusive cytoplasm and membrane staining (B; magnification 200×, and 400× in box on right).

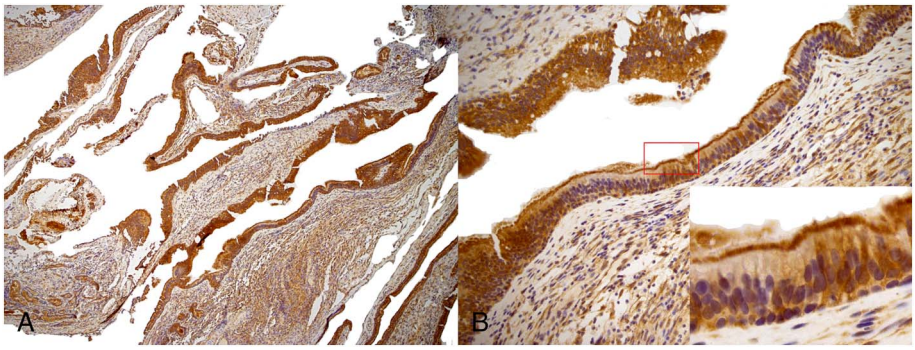

Fig. 4. Representative case of non-eosinophilic polyp showing strong cortactin staining (A; magnification 25×); high magnification shows exclusive cytoplasm and membrane staining (B; magnification 200×, and 400× in box on right).

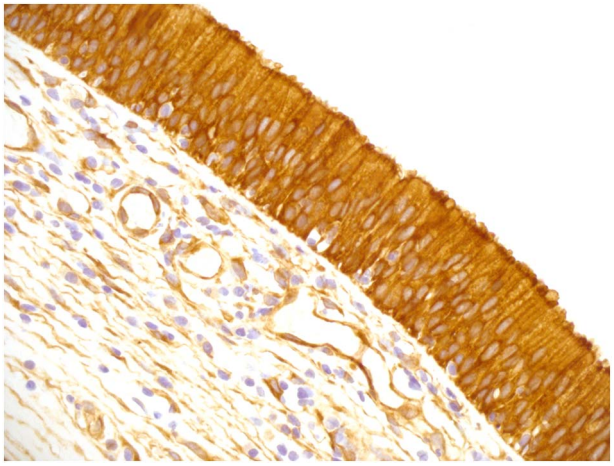

Fig. 5. Representative case of control group showing strong immunoreactivity to cortactin of nasal respiratory epithelium. Normal submucosal structures as vascular endothelium also show immunoreactivity to cortactin while resident immune cells are negative.

3. Results

3.1. Clinical, laboratory, pathological, and immunohistochemical features of the cohort of AERD patients as a whole

The cohort consisted of 18 patients with AERD (9 males and 9 females; mean age 48.0 ± 12.1 years) who underwent ESS for CRSwNP.

The blood tests identified a mean eosinophil count of 0.48 ± 0.22 cells × 10^9L, and a basophil count of 0.04 ± 0.02 cells × 10^9L, and the NLR was 1.98 ± 0.69. Spearman's rank correlation test ruled out any significant correlation between the eosinophil and basophil counts (rho = 0.18, p = 0.47), between the eosinophil count and the NLR (rho = 0.18, p = 0.48), and between the basophil count and the NLR (rho = 0.37, p = 0.13).

On histological examination, the polyps were eosinophilic in 15 patients and non-eosinophilic in 3. The mean tissue eosinophil count in the whole cohort was 20.72 ± 10.29/HPF. It correlated marginally with the blood eosinophil count (Spearman's rank correlation test, rho = 0.43, p = 0.07 [trend towards significance]), but not with the blood basophil count (Spearman's rank correlation test, rho = 0.15, p = 0.55).

3.2. Cortactin expression

In both eosinophilic and non-eosinophilic sinonasal polyps (Figs. 1 and 2, respectively), the respiratory epithelium showed a strong cytoplasmic and membranous immunoreactivity to cortactin (Figs. 3 and 4). Inside the submucosae, epithelial-derived structures comprising blood vessels and glands also showed a strong cortactin immunoreactivity, and so did activated fibroblasts, giving the polyp's stroma a fine, diffuse immunoreactive background. The immune cells included eosinophils, monocytes, lymphocytes, and plasma cells, none of which showed cortactin staining (Figs. 3 and 4). Control group specimens showed strong cytoplasmatic and membranous immunoreactivity to cortactin in columnar respiratory epithelium and in vascular endothelium; while submucosal immune cells showed negative stain to cortactin (Fig. 5).

Cortactin expression in the sinonasal polyps was scored as +3 in 17 patients, and +2 in one. Cortactin immunostaining intensity was scored as +3 in 9 patients, and +2 in 9. The H-score was +4 in 9 patients, +3 in 8, and +2 in one. When the AERD patients were stratified by cortactin immunostaining intensity (+2 vs +3), Fisher's exact test ruled out any significant difference in the distribution of the allergic versus non-allergic patients (p = 0.19). There were also no significant differences between the sub-cohorts of AERD patients with a cortactin immunostaining intensity of +2 vs +3, in terms of their mean blood eosinophil and basophil counts, or NLR (Mann–Whitney test,

Table 1
Laboratory features of AERD patients stratified by gender, allergy and prognosis.

	No. of cases (%)	NLR mean ± SD	Blood eosinophil count (cells × 10^9L) mean ± SD	Blood eosinophil % mean ± SD	Blood basophil count (cells × 10^9L) mean ± SD	Blood basophil % mean ± SD
Male	9 (50%)	1.79 ± 0.60	0.41 ± 0.19	6.07 ± 2.38	0.04 ± 0.03	0.59 ± 0.55
Female	9 (50%)	2.17 ± 0.75	0.56 ± 0.23	8.63 ± 4.33	0.04 ± 0.02	0.60 ± 0.19
[a]p-value		*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*
Allergy	11 (61%)	1.96 ± 0.68	0.45 ± 0.21	7.05 ± 3.62	0.04 ± 0.03	0.62 ± 0.48
No allergy	7 (39%)	2.01 ± 0.76	0.54 ± 0.24	7.81 ± 3.91	0.04 ± 0.02	0.56 ± 0.24
[a]p-value		*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*
Recurrence	8 (44%)	2.06 ± 0.85	0.42 ± 0.17	7.41 ± 3.66	0.04 ± 0.03	0.73 ± 0.55
No recurrence	10 (56%)	1.92 ± 0.58	0.53 ± 0.24	7.30 ± 3.82	0.04 ± 0.02	0.49 ± 0.19
[a]p-value		*n.s.*	*n.s.*	*n.s.*	*n.s.*	*n.s.*

AERD = Aspirin-exacerbated respiratory disease; NLR = neutrophil-to-lymphocyte ratio.
n.s. = not significant (p-value > 0.05 without evidence of a statistical trend); SD = standard deviation.
[a] Mann–Whitney test.

p > 0.05).

3.3. Features of AERD patients by gender

The Mann–Whitney test ruled out any significant differences between male and female patients in terms of their blood eosinophil and basophil counts, or NLR (Table 1).

On the other hand, a trend emerged towards a significantly higher cortactin expression and H-score in female AERD patients (Fisher's exact test, p = 0.05 in both cases) (Table 2).

3.4. Features of AERD patients and allergy

Concomitant allergy was identified in 11 AERD patients, most of them male (8 out of 11; Fisher's exact test, p = 0.02). Statistical analysis ruled out any significant difference between these patients and those without allergy, in terms of their blood eosinophil and basophil counts, and NLR (Table 1). The sub-cohort of patients with allergy was not more likely to develop recurrent polyps than the group without allergy (Fisher's exact test, p > 0.05).

Fisher's exact test ruled out any significant differences in the distributions of cortactin expression, cortactin immunostaining intensity, and H-score between the AERD patients with and without concomitant allergy (Table 2).

3.5. Features of CRSwNP and AERD with and without recurrent disease after ESS

Recurrent CRSwNP was identified endoscopically in 8 cases of the cohort considered. No significant differences came to light, in terms of blood eosinophil and basophil counts, or NLR, when patients who developed a recurrence were compared with those who did not (Table 1).

Statistical analysis ruled out any significant difference in cortactin expression, cortactin immunostaining intensity, and H-score distributions between AERD patients with and without recurrent disease after ESS (Table 2).

4. Discussion

AERD is seen as a specific CRSwNP endotype nowadays because of its known pathogenesis, which is characterized by a dysregulation in arachidonic acid metabolism, reflecting diminished levels of anti-inflammatory prostaglandin E2 and higher levels of 5-lipoxygenase products such as leukotrienes C4, D4, and E4[21]. In the present study, we only classified patients as cases of AERD if they had CRSwNP and asthma, and they developed specific upper and/or lower respiratory tract reactions to COX-1 inhibitors. Stevens et al. [1] reported a 16% prevalence of AERD among patients with CRSwNP. Atopy is significantly more prevalent in patients with AERD (84%) or asthma (85%), than in those with other CRSwNP endotypes (66%) [1]. In AERD patients, asthma is severe and difficult to treat, as is the sinus disease component [2]. According to Stevens et al. [1], AERD patients also undergo sinus surgery twice as often as patients with other CRSwNP endotypes, and they are significantly younger at the time of their first surgical procedure. The information available on AERD epidemiology is somewhat confusing. Kennedy et al. [2] found that AERD mostly affected males, but was more aggressive in female patients, whereas Stevens et al. [1] identified a higher prevalence of AERD in females. In our cohort of AERD patients, there were no differences in gender distribution or gender-associated prognosis. Generally speaking, the clinical course of AERD is more aggressive than in patients who have CRSwNP and asthma, but are not intolerant of COX-1 inhibitors. As Kennedy et al. reported [2], an additional feature of nasal polyps in AERD lies in the eosinophilic histotype being associated with blood hypereosinophilia. In our cohort, the mean tissue eosinophil count revealed only a marginal direct correlation with the blood eosinophil

Table 2
Cortactin expression in nasal polyps; cohort stratified by gender, allergy and prognosis.

	No. of cases (%)	Cortactin expression (No. of cases)			Cortactin immunostaining intensity (No. of cases)			H-score (No. of cases)		
		+1	+2	+3	+1	+2	+3	+2	+3	+4
Male	9 (50%)	0	1	8	0	7	2	1	6	2
Female	9 (50%)	0	0	9	0	2	7	0	2	7
[a]p-value		*1*			*0.05*			*0.05*		
Allergy	11 (61%)	0	1	10	0	7	4	1	6	4
No allergy	7 (39%)	0	0	7	0	2	5	0	2	5
[a]p-value		*1*			*0.19*			*0.63*		
Recurrence	8 (44%)	0	0	8	0	3	5	0	3	5
No recurrence	10 (56%)	0	1	9	0	6	4	1	5	4
[a]p-value		*1*			*0.39*			*0.39*		

H-score: (1+ intensity) / (3 × expression score).
[a] Fisher's exact test.

count (p = 0.07).

Cortactin has been widely investigated in neoplastic diseases, and found involved in tumor progression and metastasis [4,6,9]. Recent studies have investigated the role of cortactin in inflammatory diseases, and particularly its function in human airways. In this specific area of research, the main studies on cortactin focused on asthma and asthma-related disorders. Mucus hypersecretion is an important manifestation of obstructive airway diseases, such as chronic obstructive pulmonary disease and asthma. Liu et al. [14] found a cortactin-mediated mucin hypersecretion from human airway epithelial cells in high shear stress conditions due to bronchoconstriction; they concluded that cortactin was significantly involved in the inflammatory process. Cortactin interaction with Profilin-1 (Pfn-1), an actin-regulating protein that has a role in modulating smooth muscle contraction, is essential for smooth muscle contraction to regulate the active dynamics in the human airway. The linkage between cortactin and Pfn-1 under stimulation by acetylcholine seems to induce smooth muscle hyper-contractility, and consequent airway hyper-responsiveness, whereas cortactin depletion results in a weaker contractile response from the human bronchial rings [15]. Cortactin therefore seems to be involved in both mucus hypersecretion and the bronchoconstriction process. The cortactin gene has also been found to contain severe asthma susceptibility polymorphisms [22], as the 11q13 chromosomal region includes at least five asthma-related genes [23].

The main aim of the present study was to examine cortactin expression in the nasal polyps of a consecutive cohort of AERD patients. Its main strength lies in the homogeneity of the series of patients considered as regards the following aspects: (i) the same team of surgeons decided whether ESS was indicated; (ii) the histological diagnosis was established by the same pathologist; (iii) the same team conducted the endoscopic follow-up for at least a year; (iv) recurrent CRSwNP was always confirmed endoscopically; and (v) all laboratory tests were performed at the same laboratory. The main limitations of the study regard its retrospective setting and the limited number of patients involved.

As mentioned previously, the eosinophilic CRSwNP histotype is prevalent in AERD patients, and it accounted for 83.3% of our cohort. Concomitant allergy was found in more than 60% of our sample, and was diagnosed significantly more often in males than in females (89% vs 33%). Kennedy et al. [2] reported frequently finding no atopy in AERD patients, presumably due to the fact that evidence of specific IgE sensitization was often lacking. Stevens et al. [1], on the other hand, found that 84% of their AERD cases positive for allergy.

Among our AERD patients, the CRSwNP recurrence rate was 44%, but the patients with allergy were no more likely to have recurrent polyps than the group without allergy. Cortactin was strongly expressed in the epithelial component and fibroblasts of the nasal polyps, but statistical analysis ruled out any significant difference in cortactin expression, cortactin immunostaining intensity or H-score distributions between AERD patients with and without recurrent disease after ESS. Cortactin expression levels were higher in female patients, and this could relate to AERD being more aggressive in females, as reported by other authors [2]. Although the recurrence rate did not differ between genders in our series, further studies are warranted to investigate whether this reported difference in AERD aggressiveness might be cortactin-mediated.

In conclusion, AERD is a complicated inflammatory disease associated with a dysregulation of eicosanoid metabolism, and of activated effector cells, including eosinophils, basophils, T helper cells-2, innate lymphocyte cells-2, and respiratory epithelial cells. The treatment for the less severe forms of AERD involves sinus surgery and the use of topical and oral steroids, long-acting beta-agonists, and anti-leukotriene drugs. Aspirin desensitization and high-dose aspirin therapy are still the mainstay of therapy for moderate-to-severe AERD [24]. The role of biological agents such as anti-interleukin agents in the management of AERD remains to be seen. Cortactin expression was certainly high in the nasal polyps of our AERD patients (+3 in 17/18 cases), in both the epithelial cells and the fibroblasts. This cortactin upregulation in AERD patients' polyps supports the hypothesis that inhibiting cortactin's functions could have selective, at least local, effects. Prospective studies should be designed to further investigate the role of cortactin in the biology of AERD, and the feasibility of using cortactin-targeted approaches integrated in the treatment of AERD.

Conflict of interest and source of funding

No conflict of interest to declare.

This study was partly supported by grant No. DOR 1658072/16 (G. Marioni) from the University of Padova, Italy.

Acknowledgments

The authors thank Frances Coburn for correcting the English version of this paper.

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