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Otitis media with effusion in aspirin-exacerbated respiratory disease patients—A series of 22 cases

1 | INTRODUCTION

Aspirin-exacerbated respiratory disease (AERD) or Samter's triad is a combination of eosinophilic nasal polyps, aspirin sensitivity and non-atopic asthma, first described by Widal in 1922.¹ Nasal polyps and asthma are frequently more severe and resistant to treatment in patients with additional aspirin sensitivity. Caversaccio et al² further proposed that patients with AERD are more likely to develop otitis media with effusion (OME) than other nasal polyp and asthma patients, the risk being about 26%. In another study, the risk for OME in AERD patients was estimated to be five times higher than the risk in patients with only nasal polyps.³

OME is a condition defined as chronic inflammation of the mucosa with retention of fluid in the middle ear. Adding OME to AERD results in the more severe form, "Samter's quad." In most cases, OME develops subsequent to the onset of the other manifestations. All previous studies agree that the ear pathology is an outcome of the underlying mucosal inflammation itself rather than Eustachian tube dysfunction.^{2,4-6} Lately, more information has

accumulated about a middle ear disease characterised by the accumulation of eosinophils in the middle ear called eosinophilic otitis media (EOM). EOM is associated with asthma and nasal polyps but not necessarily with aspirin intolerance.⁷

To our knowledge, there are only a few published reports in English describing otological manifestations specifically in AERD; there are three case reports, and two original publications with a series of two and six patients.^{2,4-6,8} We describe the largest series to date of 22 AERD patients with OME. We retrospectively assessed the symptoms, treatment and outcome of these patients to characterise the course of the disease, and to see whether any treatment modality would appear superior.

2 | MATERIALS AND METHODS

2.1 | Ethical considerations

The study was approved by the Research Ethics Board of Helsinki University Hospital.

2.2 | Patients

The patient charts of all patients treated for OME associated with AERD at Helsinki University Hospital from January 2014 to May 2017 were reviewed. The data recorded included gender, age, duration of symptoms, dates of diagnoses, duration of follow-up, type, number and outcome of rhinologic and otologic surgeries, hearing levels, medications used, available eosinophilic levels in the blood, middle ear fluid, and in mucosa, and possible aspirin desensitisation therapies.

3 | RESULTS

Twenty-two patients (fifteen females and seven males, mean age 53 years, median age 56.5 years, range 27-75) with a diagnosis of OME in association with asthma, nasal polyps and aspirin sensitivity were retrieved. Table 1 shows that the average retrospective follow-up time was 18 years (range 4-34 years).

All the patients had had nasal polypectomy performed at least once, and all of them except one, had undergone endoscopic sinus surgery at least once. Seventeen patients had been treated with extended sinus surgery and four patients with only middle meatal antrostomy and anterior ethmoidectomy.

All the patients had suffered from recurrent periods of OME, and all had had bilateral symptoms. In addition, all except two had had tympanostomy tubes inserted at least once, and 19 had had spontaneous perforations of their tympanic membranes with ear discharge. Of the patients treated with tympanostomy tubes ($N = 20$), 17 had a post-tympanostomy tube perforation, some of these had healed spontaneously, but 11 patients had a persistent perforation. Two patients had bilateral persistent perforations. Multiple bacteria were found in middle ear bacterial cultures, the most common being *Staphylococcus aureus* (16/22 patients, 73%).

Six patients had undergone mastoidectomy, one of them bilaterally, due to chronic mastoiditis (Figure 1). Only one patient (No. 8) remained free of ear discharge postoperatively. Her symptom-free period is now a little over 2 years. In the others, the symptom-free period has varied post-operatively from 2 months to 2 years.

Fourteen patients had reduced hearing ($PTA < 30$ dB) with significant air-bone gaps, and six of them used hearing aids. Two patients (No. 3 and No. 5) had sudden sensorineural hearing loss during a prolonged period of ear discharge, and hearing has not recovered in either of their ears.

In total, six middle ear mucosal samples, and four middle ear effusion samples were obtained. The pathological evaluation showed minor eosinophilia in one middle ear mucosal sample (No. 16), and in three middle ear discharge samples. In contrast, pathological evaluation showed nasal eosinophilic polyposis in the samples of 21 patients, and 19 patients had had high blood eosinophilia counts at least once at some point during the follow-up period.

During the study period, two patients received anti-IL5-treatment (mepolizumab, Nucala[®]) for severe asthma, and they both had continuous ear

Keypoints

- Otitis media with effusion associated with aspirin-exacerbated respiratory disease is a difficult entity to treat.
- Mastoid or middle ear surgery rarely results in a permanent cure.
- Spontaneous but temporary recovery often occurs.
- Sensorineural hearing loss may result from recurrent or prolonged ear discharge.
- Otitis media with effusion often develops subsequent to the other manifestations of aspirin-exacerbated respiratory disease.

discharge during the treatment. No clear improvement in their ear symptoms during a course of six doses of anti-IL5 treatments was observed.

Twelve patients received aspirin desensitisation therapy at some point. Two of them did not tolerate the therapy and it had to be discontinued, and the rest did not gain any substantial benefit that alleviated asthma, nasal polyps or OME.

4 | DISCUSSION

Chronic OME presents an additional challenge to the already demanding treatments available for AERD patients. Extensive surgery and conservative therapy have both been suggested but the number of patients studied is small.^{4,8} According to our experience, mastoidectomy gives only temporary relief. Only one of seven operated ears in our series has been symptom free since the operation. Therefore, we suggest a watch and wait policy and conservative treatment with topical corticosteroids and antibiotics as required by the results of the patients' bacterial cultures, when necessary. In addition, to the difficulties associated with the disease, it has a natural tendency to exhibit variability and spontaneous, even though often temporary, recovery can occur.

Eosinophilic otitis media (EOM) is a recently established disease characterised by the accumulation of eosinophils into middle ear effusion or mucosa. It is associated with asthma and nasal polyposis. The diagnostic criteria for EOM are eosinophil dominant effusion with two or more of the following: highly viscous middle ear effusion, resistance to conventional treatment, bronchial asthma and nasal polyps.⁷ All our AERD patients with OME fulfilled the four minor criteria but we detected only minimal eosinophilia in four of their middle ear effusion or mucosal samples. However, not every patient had a representative sample taken.

Patients with OME have conductive hearing loss due to mucosal swelling and effusion in the middle ear. However, patients with AERD and OME have been reported to develop sensorineural hearing loss, as well.^{4,5} In our study, most patients' hearing loss was conductive but we had two patients who developed a sudden, profound unilateral sensorineural hearing loss during prolonged ear discharge.

TABLE 1 Patient characteristics for 22 patients with asthma, nasal polyps, aspirin intolerance and otitis media with effusion (OME)

Patient	Sex (M/F)	Age (years)	Follow-up (years)	Age at onset of Asthma	Age at onset of Nasal polyps	Age at onset of Aspirin Hypersensitivity	Age at onset of Otolological Manifestations	Polypectomy (N)	FESS (N)	Caldwell Luc Surgery	Tympanostomy	Perforation of the tympanic membrane	Mastoidectomy
1	M	42	13	MI	20	34	33	7	1	Yes	10	Both	Yes, right
2	F	27	6	19	20	19	1	2	1	No	0	Both	No
3	F	40	23	13	15	14	30	3	2	No	14	Both	Yes, left
4	M	52	12	MI	MI	MI	MI	4	1	No	3	Both	No
5	F	54	34	17	24	20	25	7	3	Yes	8	Both	No
6	F	61	32	31	29	MI	MI	2		Yes	1	Both	No
7	F	71	19	33	50	40		1	1	Yes	1	Both	No
8	F	64	28	32	33	18	32	5	1	Yes	12	Both	Yes, right
9	F	49	25	31	31	31	35	9	5	No	8	Right	Yes, right
10	M	62	34	36	30	MI	60	3	2	No	3	No	No
11	F	75	15	33	60	60	71	4	1	No	0	Right	No
12	F	66	29	25	25	MI	44	3		No	11	Both	No
13	F	69	12	28	28	28	41	1	2	Yes	5	Both	Yes, right and left
14	M	66	30	37	37	53	44	7	4	Yes	2	Both	Yes, right
15	F	62	11	33	41	48	51	3	3	No	3	Both	No
16	M	49	12	3	8	38	34	3	3	Yes	3	Both	No
17	M	37	4	30	29	MI	36	1	2	No	1	No	No
18	F	62	22	41	41	43	44	4	1	Yes	3	Both	No
19	F	37	12	6	25	29	36	5	2	No	7	Both	No
20	F	59	9	49	50	52	49	2	2	No	1	Left	No
21	M	28	6	21	21	25	28	1	2	No	1	No	No
22	F	39	12	20	22	21	37	2	2	No	3	Right	No
Mean		53.2	18.2	26.9	30.4	33.7	38.5	3.6	2.1		4.5		
N	F = 15, M = 7							22	20	9	20	19	6
Median		56.5	14.0	30.5	29.0	31.0	36.0	3.0	2.0		3.0		

M, male; F, female; N, number; FESS, functional endoscopic sinus surgery; PTA, pure tone average (average of 0.5 kHz, 1 kHz, 2 kHz, 4 kHz); dB, decibel; MI, missing information.

Non-discharge period after mastoidectomy	PTA right/left (dB)	Air-bone gap (dB)	Hearing aid	Aspirin desensitisation	Pathological anatomical diagnosis	Eosinophilia in middle ear fluid	Eosinophilia in middle ear mucosa sample	Blood eosinophilia	Smoking	Bacteria in middle ear fluid
2 months	44/25	5-45 both	No	Yes	Nasal polyps with eosinophilia	Yes	No	Yes	Yes	<i>Staphylococcus aureus</i> , <i>Streptococcus pneumoniae</i>
	29/24	10-40 both	No	No	Nasal polyps with eosinophilia	MI	MI	Yes	Never	<i>Klebsiella oxytoca</i>
5 months	20/102	15-25 right	No	Yes	Nasal polyps with eosinophilia	MI	No	Yes	Never	<i>Staphylococcus aureus</i>
	15/16	0	No	Failed	Nasal polyps with eosinophilia	MI	MI	MI	Ex-smoker	<i>Staphylococcus aureus</i>
	deaf/41	10-25 left	Yes	Yes	Nasal polyps with eosinophilia	MI	MI	Yes	Never	<i>Staphylococcus aureus</i> , <i>Pseudomonas aeruginosa</i> , <i>Streptococcus pneumoniae</i> , <i>Hemophilus influenzae</i> , <i>Moraxella catarrhalis</i> , <i>Enterobacter cloacae</i>
	43/14	10-30 both	No	MI	Nasal polyps with eosinophilia	MI	No	No	Ex-smoker	<i>Staphylococcus aureus</i> , <i>Streptococcus pneumoniae</i>
	35/69	10-30 both	Yes	Yes	Nasal polyps with eosinophilia	MI	MI	Yes	Never	<i>Staphylococcus aureus</i> , <i>Hemophilus influenzae</i> , <i>Pseudomonas aeruginosa</i> , <i>Acinetobacter</i>
Permanently	45/33	0-45 both	Yes	No	Nasal polyps with eosinophilia	No	No	Yes	Ex-smoker	<i>Staphylococcus aureus</i> , <i>Streptococcus pneumoniae</i> , <i>Moraxella catarrhalis</i> , <i>Pseudomonas aeruginosa</i> , <i>Hemophilus influenzae</i> , <i>Streptococcus viridans</i> , <i>Klebsiella pneumoniae</i> , Group b and g streptococcus
2 months	23/20	0-40 right	No	Yes	Nasal polyps with eosinophilia	MI	MI	Yes	Ex-smoker	<i>Staphylococcus aureus</i>
	MI	MI	No	No	Nasal polyps with eosinophilia	MI	MI	Yes	Never	<i>Hemophilus influenzae</i> , <i>Staphylococcus aureus</i>
	41/27	10-30 right	No	No	Nasal polyps with eosinophilia	Yes	MI	Yes	Never	<i>Staphylococcus aureus</i> , <i>Streptococcus agalactiae</i> , <i>Fusobacterium necrophorum</i>
	43/44	0	No	No	Nasal polyps with eosinophilia	MI	MI	Yes	Never	<i>Pseudomonas aeruginosa</i> , <i>Staphylococcus aureus</i> , <i>Staphylococcus epidermidis</i>
1 year	45/35	0-35 both	Yes	Yes	Nasal polyps with eosinophilia	Yes	No	Yes	Never	<i>Staphylococcus aureus</i> , <i>Moraxella catarrhalis</i> , <i>Escherichia coli</i>
2 years	40/25	0-25 both	No	Yes	Nasal polyps with eosinophilia	MI	MI	Yes	Never	MI
	31/39	10 both	No	Failed	Nasal polyps with eosinophilia	MI	MI	Yes	Ex-smoker	<i>Staphylococcus aureus</i>
	21/33	10-30 both	No	No	Nasal polyps with eosinophilia	MI	Yes	Yes	Never	<i>Klebsiella oxytoca</i> , Group b and g streptococcus, <i>Pseudomonas aeruginosa</i> , <i>Streptococcus pneumoniae</i> , <i>Staphylococcus aureus</i>
	Normal	0	No	Yes	Nasal polyps with eosinophilia	MI	MI	Yes	Ex-smoker	<i>Escherichia coli</i>
	33/39	0-30 both	Yes	No	Nasal polyps with eosinophilia	MI	MI	No	Never	<i>Escherichia coli</i> , <i>Staphylococcus aureus</i>
	MI	MI	No	No	Nasal polyps with eosinophilia	MI	MI	Yes	Never	<i>Staphylococcus aureus</i>
	49/43	20-30 both	Yes	No	Inflammation in mucosa	MI	MI	Yes	Never	<i>Pseudomonas aeruginosa</i> , <i>Serratia marcescens</i>
	11/10	0	No	Yes	Nasal polyps with eosinophilia	MI	MI	Yes	Ex-smoker	-
	5/3	0	No	Yes	Nasal polyps with eosinophilia	MI	MI	Yes	Never	<i>Staphylococcus aureus</i>
			6	12			3/4	1/6	19	1

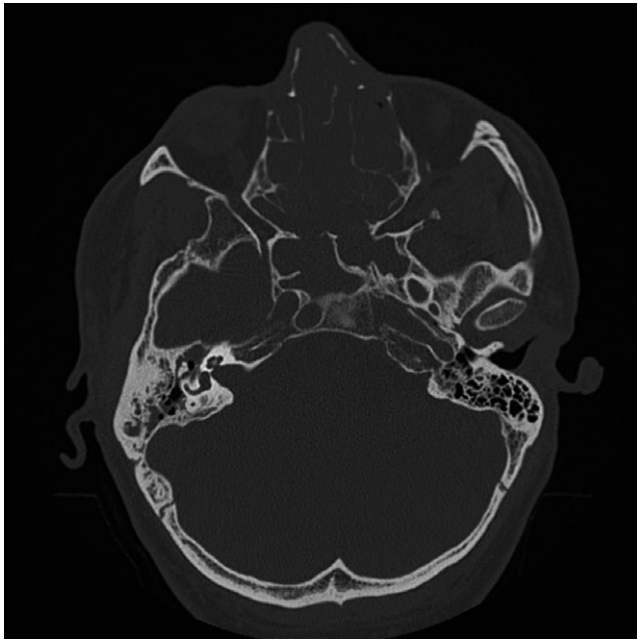


FIGURE 1 CT-scan of a patient with severe polyposis of the nasal and sinonasal cavities. Effusion in the middle ear and the right mastoid

The same patients had earlier suffered from episodes of ear discharge without any sensorineural hearing loss. Precautions must be taken when treating these patients, and it is important to evaluate and constantly monitor their hearing acuity by audiometry. The mechanism behind the cascade leading to sensorineural hearing loss is not understood.

Staphylococcus aureus is often involved in prolonged ear discharge. In our series, 73% of patients had had positive bacterial cultures for *Staphylococcus aureus* at some point. We recommend repetitive bacterial cultures and appropriate antibiotic treatment guided by them. If only normal flora is found, treatment with topical steroids alone should be considered.

Overall, more studies are needed to understand OME associated with AERD, its treatment and outcome. Immunological responses may vary due to environmental factors, and factors associated with patient variability. However, it seems that OME is often the last component of the quartet that develops.

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CONFLICT OF INTEREST

The authors have no conflicts of interest relating to this article.

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