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Association of *Pseudomonas aeruginosa* Infection with Histopathological Changes of the Middle Ear Mucosa and Degree of Otorrhea in Patients with Benign Chronic Suppurative Otitis Media

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ABSTRACT

Background: Chronic Suppurative Otitis Media (CSOM) is a chronic inflammatory disease of the middle ear characterized by otorrhea due to tympanic membrane perforation. The most common bacterial infection is caused by *Pseudomonas aeruginosa*. The mucosa and cilia of the middle ear may be damaged by toxins produced by this bacterium, leading to tissue-level damage.

Objective: This study aimed to analyze the association between *Pseudomonas aeruginosa* infection and histopathological changes of middle ear mucosa as well as the degree of otorrhea in patients with benign CSOM.

Methods: This was an observational study with a cross-sectional design. Samples were collected using consecutive sampling from patients with benign CSOM who underwent tympanoplasty at Dr. Kariadi General Hospital. The degree of otorrhea was assessed using otoscopy. Middle ear mucosa specimens were obtained from the promontorium and examined for microbiological culture and histopathological changes.

Results: A total of 43 subjects were included, with *Pseudomonas aeruginosa* infection in 53.6% and non-*Pseudomonas aeruginosa* infection in 46.4%. The degree of otorrhea was classified as severe (39.5%), moderate (27.9%), and mild (32.6%). Statistical analysis revealed a significant association between *Pseudomonas* infection and the degree of otorrhea ($p < 0.05$).

Conclusion: *Pseudomonas aeruginosa* infection is associated with the degree of otorrhea; however, it is not associated with histopathological changes in benign CSOM.

INTRODUCTION

Chronic Suppurative Otitis Media (CSOM) is a chronic inflammation of the middle ear and mastoid cavity characterized by recurrent ear discharge (otorrhea) due to perforation of the tympanic membrane.[12] CSOM is caused by various factors including eustachian tube dysfunction, genetics, allergy, infection, environment, social factors, and race.[3] The prevalence of CSOM in both developed and developing countries varies between 3% and 57%. In Indonesia, the prevalence of CSOM is 3.9% and accounts for 25% of patients attending ENT clinics, which represents a significant number. A national survey on vision and hearing health reported that the prevalence of CSOM was 3.1%, with benign type CSOM at 3% and malignant type at 2%.

The causative bacteria of CSOM vary. In benign CSOM patients, Gram-positive bacteria such as *Staphylococcus aureus* were found in 29.2%, Gram-negative bacteria such as *Pseudomonas aeruginosa* in 28.3%, fungi in 1.8%, and anaerobic bacteria in 3.5%. A study in Bangladesh reported *Pseudomonas aeruginosa* in 42% of cases, while *Staphylococcus aureus* accounted for only 24%. At Dr. Kariadi General Hospital, Semarang, the most common bacterium found was *Pseudomonas aeruginosa* (40.4%), while non-*Pseudomonas aeruginosa* bacteria were 59.6%.

Toxins from *Pseudomonas aeruginosa* can increase metaplasia, necrosis, and apoptosis of middle ear epithelial cells, and erode the submucosal layer down to the lamina propria, thereby causing inner ear damage. *Pseudomonas aeruginosa* infections are associated with high morbidity and mortality, particularly in vulnerable patients.[1] Moreover, antibiotic resistance in *Pseudomonas* infections complicates treatment, especially in children.[11]

The characteristics of benign CSOM include increased expression of TLR-2 and TLR-4 in the mucosa of the tympanic cavity, elevated TNF-α and IL-6 levels in middle ear secretions, as well as increased expression in the middle ear epithelium. Upregulation of TLR-2, TLR-4, TNF-α, and IL-6 is one of the tissue response mechanisms to bacterial infections such as *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Elevated TNF-α and IL-6 induce goblet cell hyperplasia and hypersecretion, as well as stimulation of mucin genes such as MUC2, MUC5, MUC5B, and MUC5AC. Excessive activation of the mucin production pathway through TLR2/4–TNF-α/IL-6–MUC/goblet cells leads to overproduction of mucin beyond normal levels, which then exits through the tympanic membrane perforation into the external ear canal (otorrhea).[12]

To date, no study has investigated the association between bacterial pathogens of CSOM with histopathological changes in the middle ear mucosa and the degree of otorrhea in patients at Dr. Kariadi General Hospital, Semarang.

METHODS

This study was an observational analytic study with a cross-sectional design. A total of 43 patients with chronic suppurative otitis media (CSOM) who were scheduled to undergo tympanoplasty at Dr. Kariadi General Hospital were included. Eligible participants were men or women aged 18 to 60 years who had not received topical or systemic antibiotics for at least 14 days prior to middle ear tissue sampling. Patients with

cholesteatoma, a history of tympanomastoidectomy, or congenital abnormalities such as cleft palate were excluded.

The severity of otorrhea was assessed by otoscopic examination of the ear cavity and classified as severe when discharge covered the entire tympanic membrane, moderate when discharge covered part of the tympanic membrane, and mild when discharge did not cover the tympanic membrane. Middle ear mucosal tissue was obtained intraoperatively from the promontory under general anesthesia. Specimens were placed in nutrient broth and biopsy preparation tubes and subsequently sent to the microbiology laboratory for bacterial culture and to the anatomical pathology laboratory for histopathological examination.

Histopathological evaluation included goblet cell hyperplasia, submucosal gland formation, and infiltration of inflammatory cells. Goblet cell hyperplasia was graded as Grade 0 (<3 cells per high-power field [HPF]), Grade 1 (3–10 cells/HPF), Grade 2 (11–20 cells/HPF), and Grade 3 (>20 cells/HPF). Submucosal gland formation was classified as Grade 0 (<3 glands/HPF), Grade 1 (3–11 glands/HPF), Grade 2 (11–30 glands/HPF), and Grade 3 (>30 glands/HPF). Inflammatory cell infiltration was assessed separately: eosinophils were graded as 0 (none), 1 (1–2/HPF), 2 (3–10/HPF), 3 (11–30/HPF), and 4 (>30/HPF); lymphocytes as 0 (<20/HPF), 1 (21–50/HPF), 2 (51–80/HPF), 3 (81–120/HPF), and 4 (>120/HPF); and PMN/neutrophils as 0 (none), 1 (1–2/HPF), 2 (3–10/HPF), and 3 (>10/HPF).

Data analysis was performed using Spearman's correlation test, with statistical significance set at $p < 0.05$. Ethical approval for this study was obtained from the Health Research Ethics Committee of Dr. Kariadi General Hospital, Semarang (No. 1141/EC/KEPK-RSDK/2022).

RESULTS AND DISCUSSION

The study analyzed data from 43 patients with benign chronic suppurative otitis media (CSOM). The youngest patient was 18 years old and the oldest was 60 years, with most participants being under 40 years of age (40.8%). The mean age was 34.35 years. The majority of subjects were female (32 patients, 74.4%).

Table 1. Characteristics of subjects with benign CSOM

Variable	n	%
Gender		
Male	11	25.6
Female	32	74.4
Disease duration		
< 5 years	24	55.8
≥ 5 years	19	44.2
Cigarette smoke exposure		
Light	42	97.7
Moderate–Severe	1	2.3
Rhinitis		
No	40	93.0
Yes	3	7.0
Bacterial infection		
Pseudomonas aeruginosa	23	53.5
Non-*Pseudomonas aeruginosa*	20	46.5
Otorrhea severity		
Mild	14	32.6
Moderate	12	27.9
Severe	17	39.5
Total	43	100.0

Most patients had a disease duration of less than 5 years (24 subjects, 55.8%). Light exposure to cigarette smoke was the most dominant risk factor (95.9%), and most patients did not have rhinitis (42 subjects, 97.7%). Pseudomonas aeruginosa was identified in 23 patients (53.6%). Regarding the severity of otorrhea, most patients fell into the severe category (17 subjects, 39.5%).

Table 2. Association between *Pseudomonas aeruginosa* infection and histopathological changes

Variable	p	rho
Goblet cell hyperplasia	0.738	-0.053
Submucosal gland formation	0.445	-0.120
Eosinophil infiltration	0.580	0.087
Neutrophil infiltration	0.902	-0.019

*Significant at $p < 0.05$

Table 2 shows that there was a negative correlation between *Pseudomonas aeruginosa* infection and goblet cell hyperplasia ($p = 0.738$, rho = –0.053). Negative correlations were also observed between *Pseudomonas aeruginosa* infection and submucosal gland formation ($p = 0.445$, rho = –0.120). Infiltration of inflammatory cells (eosinophils, lymphocytes, and neutrophils) was not significantly associated with infection ($p = 0.580$, $p = 0.306$, $p = 0.902$). However, a significant moderate correlation was found between *Pseudomonas aeruginosa* infection and the degree of otorrhea ($p = 0.005$, rho = 0.420).

Regarding confounding variables, such as sex, disease duration, and cigarette smoke exposure, no significant association was observed with histopathological changes ($p > 0.05$). However, rhinitis was found to be associated with neutrophil infiltration, showing a weak positive correlation ($p < 0.05$, rho = 0.373).

In this study, 53.5% of cases with Pseudomonas aeruginosa infection were significantly associated with the degree of otorrhea ($p = 0.005$, rho = 0.420), in contrast to non–Pseudomonas aeruginosa infections, where otorrhea was predominantly mild. Pseudomonas aeruginosa is one of the bacteria that increases the severity of otorrhea. Its resistance to antibiotics is a strong factor explaining why this bacterium contributes to higher otorrhea severity.[12] Other bacteria that can also increase otorrhea severity include Streptococcus pneumoniae, Haemophilus influenzae, and Staphylococcus aureus. Increased expression of TLR-2, TLR-4, TNF-α, and IL-6 is part of the mucosal response to bacterial invasion such as Pseudomonas aeruginosa and Staphylococcus aureus. The effect of TNF-α and IL-6 upregulation is goblet cell hyperplasia, hypersecretion, and stimulation of mucin genes (MUC2, MUC5, MUC5B, and MUC5AC). Overactivation of the mucin production pathway (TLR2/4–TNF-α/IL-6–MUC/goblet cell) increases mucin production. Mucin mixed with bacteria and mucosal debris exits through tympanic membrane perforation into the ear canal (otorrhea).[4,12,14]

The epithelial defense mechanisms of the middle ear against pathogens consist of innate and adaptive immune responses. Innate immune components include ciliated cells (mucociliary transport), secretory cells (secretion of defensins, mucins, lysozyme), neutrophils, macrophages, dendritic cells, NK cells, and pattern-recognition receptors (PRRs). Excessive cytokine production

may damage the mucosa itself. This study showed no significant relationship between Pseudomonas aeruginosa infection and goblet cell hyperplasia, submucosal gland formation, or infiltration of inflammatory cells (eosinophils, lymphocytes, and neutrophils). These findings suggest that both Pseudomonas aeruginosa and non–Pseudomonas aeruginosa infections are not associated with histopathological changes in patients with benign CSOM. Individual immune variability may also influence the process of cellular regeneration.

This study also analyzed several risk factors, including disease duration, cigarette smoke exposure, and rhinitis. Among the three subjects with CSOM and rhinitis, most showed histopathological changes in submucosal gland formation (2 subjects, 66.7%) and inflammatory cell infiltration (1 subject, 33.3%). Patients with allergies had a higher incidence of chronic otitis media than those without allergies, supporting the role of allergy or atopy as a significant risk factor for CSOM. The middle ear mucosa shares immunological characteristics with the upper respiratory tract mucosa, supporting the concept of the unified airway.[15] Rhinosinusitis is a chronic inflammation of the nasal cavity and paranasal sinus mucosa. Inflammation causes edema of the nasopharyngeal mucosa, Eustachian tube dysfunction, and hypertrophy of subepithelial lymphoid tissue around the tube. Consequently, tympanic cavity ventilation decreases, and middle ear secretory drainage into the nasopharynx is impaired. Rhinosinusitis has been shown to serve as a septic focus for chronic suppurative otitis media. A cohort study of 60 patients with rhinosinusitis in Chennai, India, found that 40 (66%) suffered from benign CSOM.

CONCLUSION

In this study, no association was found between *Pseudomonas aeruginosa* infection and histopathological changes in patients with benign CSOM. However, a significant association was observed between *Pseudomonas aeruginosa* infection and the degree of otorrhea in patients with benign CSOM. Further studies are needed to evaluate the morphological variations of the middle ear mucosa in CSOM patients, as these variations may influence histopathological assessment.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest with any private, public, or academic parties related to the information presented in this manuscript.

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