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Postoperative Pneumonia After Esophagectomy and Systemic Inflammatory Response Syndrome

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Abstract. *Background/Aim: The aim of this study was to determine the association between post-esophagectomy pneumonia and the presence of pathogenic organisms in the sputum or pharynx and postoperative systemic inflammatory response syndrome (SIRS). Materials and Methods: This retrospective study included 98 patients diagnosed with esophageal cancer who had undergone esophagectomy. Results: Postoperative pneumonia was observed in 24 patients (24.5%). Of the total 98 patients, 45 (45.9%) were tested positive for pathogenic organisms preoperatively, and 16 of those (35.6%) developed postoperative pneumonia; postoperative pneumonia occurred at a higher rate in these patients compared to pathogenic organism-negative patients (p=0.019). Postoperative SIRS was observed in 62 patients (63.3%), and 21 of these (33.9%) developed postoperative pneumonia, a significantly higher rate compared to patients without SIRS (p=0.007). Conclusion: Postoperative pneumonia was significantly associated with the presence of pathogenic organisms in the sputum or pharynx and postoperative SIRS.*

Esophagectomy is one of the most complex invasive gastrointestinal surgeries (1), and postoperative complications are more common than with other similarly complex operations. Among such postoperative complications, pneumonia has been reported to be the most common with an incidence of 15.4-36.2% (2-6). It has also been reported that preventing postoperative pneumonia would reduce postoperative mortality in esophageal cancer (2, 6).

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The reported risk factors for pneumonia following esophagectomy include the annual number of surgical cases performed (7), pulmonary function test results, age, gender, cancer stage, primary tumor site, habits (such as drinking and smoking), history of chronic obstructive pulmonary disease, poor nutritional status, cardiac, liver, and kidney function, and operative time (8-10). However, in recent year reports from a bacteriological perspective have emerged. To be more precise, pneumonia has been associated with oral bacteria (11), and several studies have reported that postoperative pneumonia was associated with oral bacteria in patients with esophageal cancer (12). Furthermore, following a highly invasive surgery such as esophagectomy, hypercytokinemia or systemic inflammatory response syndrome (SIRS), has often been observed. It has also been reported that SIRS is often associated with various complications such as pulmonary complications (1, 13).

In the present study, to identify the cause of pneumonia following surgery for esophageal cancer, the association between postoperative pneumonia and the presence of pathogenic organisms in the sputum or pharynx and postoperative systemic inflammatory response syndrome (SIRS) was investigated.

Materials and Methods

Patients. This retrospective study included 98 patients with esophageal cancer who underwent esophagectomy at Tokyo Women's Medical University Medical Center East, between January 2008 and December 2015. All patients were diagnosed as having squamous cell carcinoma (SCC). The pathological stage was assigned according to the International Union Against Cancer's TNM classification system, 6th edition. All patients were admitted to the intensive care unit (ICU) immediately after surgery without extubation and remained on mechanical ventilation using the continuous positive airway pressure (CPAP) mode. The fractional concentration of inspired oxygen was initiated at 0.25 and was then adjusted so that the partial pressure of oxygen in the arterial blood could be maintained above 90 mmHg. Extubation was performed on Day 2 for all patients. Each patient received methylprednisolone sodium succinate at a dose of 5 mg/kg at the start of surgery, and sivelestat sodium hydrate through continuous infusion at a dose of

4.8 mg/kg/day from the time of ICU admission until Day 2 of their hospitalization. Following surgery, no patients were diagnosed with acute respiratory distress syndrome (ARDS) or required reintubation.

Culture tests and blood tests. After hospital admission, all patients underwent examination and received oral care at the department of dental surgery. Throat and sputum cultures were performed one week or less prior to the surgery, with throat culture specimens collected using the X-seed swab γ no. 1 (Eiken Chemical Co., Ltd. Tokyo) and immediately submitted for culture. Following surgery, sputum cultures were performed for patients suspected of having pneumonia and repeated daily until recovery. A patient was diagnosed with pathogen-positive bacteria after the detection of the bacteria listed in Figure 1; all other bacteria were considered indigenous bacteria. None of the patients used antibiotics preoperatively because they were asymptomatic. The blood test and arterial blood gas was conducted less than one week before the surgery.

SIRS. For five days following surgery the patients were being screened for SIRS. After examining the ICU charts, SIRS was diagnosed when two or more parameters were fulfilled in accordance with the diagnostic criteria from the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference (14). The duration of SIRS was also examined.

Postoperative complications. Pneumonia was diagnosed when the following diagnostic parameters were all observed as follows: 1) presence of respiratory symptoms such as coughing and sputum, 2) presence of an infiltrative shadow on a plain X-ray of the chest, 3) an increased WBC or a fever of >38˚C. In addition, anastomosis leakage, surgical site infection (SSI), sepsis, central venous (CV) catheter infection, enteritis, liver dysfunction (when either a GOT or GPT of >200 or hyper-bilirubinemia (serum total bilirubin level of >3.0) was observed), recurrent nerve paralysis, arrhythmia, and delirium were also assessed; anastomotic leakage, recurrent nerve paralysis, and delirium were considered Grade 2 or above according to the Clavien-Dindo classification (15).

Statistical analyses. All data are shown as mean±standard error (SEM). The statistical analyses were performed using the Student's *t*-test, Chi-square test, and Fisher's exact test. For the multivariate analyses, factors with a *p*-value of <0.1 in the univariate analyses were extracted, and an analysis was performed with a logistic regression. A *p*-value of <0.05 was considered to be significant. All analyses were performed using a statistical analysis software (JMP version 11; SAS Institute, Inc., NC, USA).

Results

Pathogenic organisms detected. Prior to surgery, the presence of pathogenic organisms (PO) was investigated in 45 patients (45.9%). The detected PO are listed in Figure 1. Data were used from the throat culture tests, which were performed in all patients, and from the sputum culture tests in 56 patients (57.1%).

In the present study, Candida was detected in 19 of the 98 patients (19.4%) and was observed preoperatively in nine (37.5%) of the 24 patients with postoperative pneumonia. In the NAC patients, Candida was observed in eight of the 25 patients (32%), which was approximately twice the rate in the non-NAC patients (15.1%). The PO that were detected preoperatively coincided with the postoperatively-detected PO in 10 of the 24 patients (41.7%).

Table I. *Patient characteristics in the two groups*.

	Postoperative pneumonia		
	Positive (n=24)	Negative (n=74)	*p*-Value
Male/female	21/3	62/12	1.000***
Age	69.5±5.9	68.4±8.5	0.536**
BMI	22.19±3.12	21.24±3.50	0.247**
Alb	3.79±0.46	3.92±0.40	0.185**
NAC			
Yes/No	8/16	17/57	0.312*
Location			
Upper, Middle/Lower	14/10	44/30	0.922*
Pathological stage			
I, II/III, IV	11/17	38/32	0.180*
Reconstruction route			
Antethoracic	1	4	0.828*
Retrosternal	15	41	
Posterior mediastinal	8	29	
Fields of lymphadenectomy			
1, 2 fields/3 fields	13/11	38/36	0.810*
%VC			
≥80%/<80%	6 /18	5/69	0.023***
FEV1.0%			
≥70%/<70%	7/17	21/53	0.941*
pO2	83.9±8.7	88.0±15.7	0.274**
Operation time	456.9±107.7	437.7±86.2	0.389**
Bleeding	706.4±475.3	600.0±356.8	0.536**
Laboratory data			
before operation			
WBC ($\times 10^3$)	6.546±1.715	5.838±1.600	0.067**
CRP	0.855±1.448	0.392±0.645	0.032**
Pathogenic bacteria positive	16	29	0.033*
SIRS patients	21	41	0.007***
SIRS patients with pathogenic			
organisms positive	14	16	0.046*

*Chi-square test; **Student's *t*-test; ***Fisher's exact test.

Patient background and postoperative complications according to the presence or absence of pneumonia. The patient background according to the presence or absence of pneumonia is shown in Table I. Postoperative pneumonia occurred in 24 of 98 patients (24.5%). Before surgery, there were 45 PO-positive patients (45.9%). Of these patients, 16 patients (35.6%) developed pneumonia postoperatively, a significantly higher incidence/rate compared to the PO-negative patients (p=0.032; odds ratio (OR)=3.1, 95% confidence interval

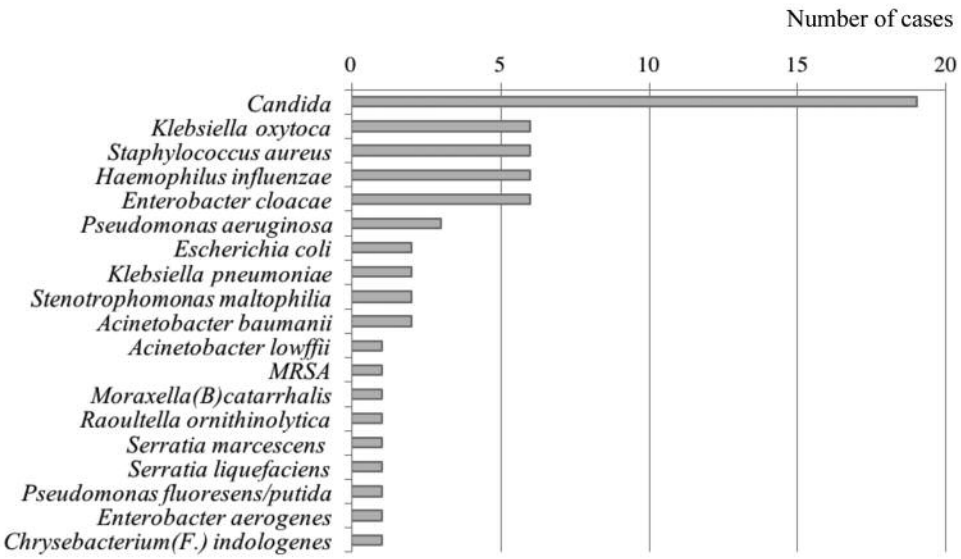

Figure 1. *Identification of pathogenic bacteria in the preoperative sputum/pharyngeal culture in all the 98 cases.*

Table II. *Complications.*

	Postoperative pneumonia		
	Positive (n=24)	Negative (n=74)	*p*-Value
Anastomotic leakage	1	1	0.43*
SSI	3	6	0.68*
Central-Venous-Catheter infection	2	1	0.15*
Infectious enteritis	2	2	0.25*
Hepatic failure	4	13	1.00*
Recurrent laryngeal nerve palsy	4	11	1.00*
Arrhythmia	6	12	0.33**
Delirium	7	14	0.29**

*χ^2 test; **Fisher's exact test.

Table III. *Multivariate analysis for clinical factor of postoperative pneumonia.*

Variables	Odds ratio	95%CI	*p*-Value
SIRS	4.84	1.42-22.52	0.0101
%VC	3.14	0.76-13.54	0.1124
Pathogenic organisms	2.13	0.71-6.57	0.1737
CRP	1.37	0.80-2.83	0.2699
WBC	1.06	0.76-1.49	0.711

(CI)=1.18-8.17). Furthermore, postoperative SIRS was observed in 62 patients (63.3%). Of these patients, 21 (33.9%) developed postoperative pneumonia, a significantly higher rate compared to the patients without SIRS (p=0.007; OR=5.63, 95%CI=1.55-20.5).

With regards to other postoperative complications, there was no significant difference observed between the two groups (Table II).

Multivariate analysis. The univariate analysis between the two groups with and without pneumonia revealed that the factors with a p-value of <0.1 included the presence or absence of PO, the presence or absence of postoperative SIRS, %VC, CRP, and WBC. Upon performing multivariate analysis (logistic analysis) using these factors, SIRS was found to be an independent predictor of pneumonia (Table III).

Association of postoperative pneumonia with SIRS and PO. While examining the time of onset of postoperative pneumonia and SIRS, it was found that in 17 of 21 patients (81%), SIRS developed 2.47±2.0 days before pneumonia (Figure 2). When the association of postoperative pneumonia with SIRS was examined according to PO, pneumonia occurred more frequently in PO-positive patients with SIRS (p=0.046; OR=5.7, 95%CI=1.1-29.7) (Table I). Also, pneumonia occurred at a higher rate in PO-negative patients with SIRS, however, the difference was not significant (p=0.126).

The number of criteria defining SIRS, SIRS duration, preoperative WBC, CRP, and neutrophil to lymphocyte ratio (N/L ratio) according to PO-positivity and–negativity. While examining the number of criteria for SIRS in patients with

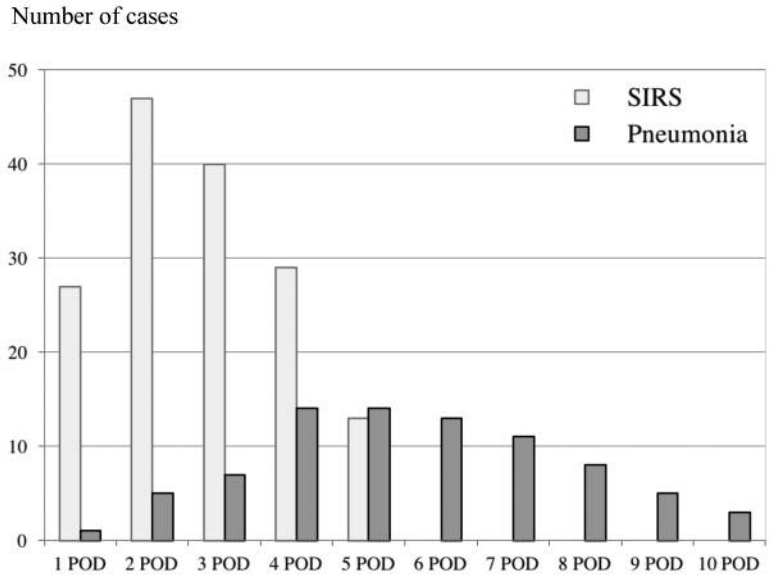

Figure 2. *Onset period of SIRS, and pneumonia.*

Table IV. *The number of positive criteria for SIRS, SIRS duration, preoperative WBC, CRP, and Neutrophil lymphocyte ratio (N/L ratio) according to pathogenic organisms-positive and -negative patients.*

	Number of positive criteria for SIRS					Duration of SIRS (h)
	1 POD	2 POD	3 POD	4 POD	5 POD	
Pathogenic organisms' positive patients (n=30)	2.92	2.48	2.39	2.21	2.33	48.0±34.1
Pathogenic organisms' negative patients (n=32)	2.27	2.42	2.18	2.20	2.25	33.0±22.2
p-Value	0.02	0.74	0.15	0.95	0.79	0.036
		WBC ($\times 10^3$/μl)		CRP (mg/dl)		N/L Ratio
Pathogenic organisms' positive patients (n=45)		6.52±1.74		0.71±1.24		3.35±1.96
Pathogenic organisms' negative patients (n=53)		5.66±1.40		0.33±0.43		2.33±1.14
p-Value		0.009		0.043		0.003

SIRS, on a postoperative day (POD)1, PO-positive patients fulfilled more criteria than PO-negative patients (2.92 *vs.* 2.27; $p=0.02$). Furthermore, the duration of SIRS was significantly longer in PO-positive patients compared to PO-negative patients (48.0 *vs.* 33.0 h; $p=0.036$). The preoperative values of WBC, CRP, and neutrophil-to-lymphocyte ratio (N/L Ratio) were significantly higher in PO-positive patients (Table IV).

Discussion

Two very interesting results were observed in the present study.

First, compared to patients without detected PO, patients with positive preoperative sputum and throat cultures had a significantly higher rate of postoperative pneumonia.

To date, oral bacteria have been considered as a major source of bacteria that cause bacterial pneumonia (11). The aspiration of oral bacteria may also be a major cause of postoperative pneumonia, and it has been reported that PO located in dental plaque, which is considered the largest bacterial reservoir in the mouth, is a major cause of aspiration pneumonia (16). Akutsu *et al.* examined pneumonia onset after surgery for esophageal cancer, and reported that patients with PO in their dental plaque had a higher incidence of postoperative pneumonia compared to

patients without PO (12). Using genetic and bacteriological approaches, El-Solh *et al*. demonstrated that PO obtained by bronchoalveolar lavage were homogenous with the PO obtained from the dental plaque culture (16). Furthermore, it has been reported that dental brushing before surgery for esophageal cancer can reduce the incidence of pneumonia following the surgery (17). This led us to hypothesize that there is a strong association between the presence of oral bacteria and the onset of pneumonia following surgery for esophageal cancer; however, there have been no reports of preoperative oral bacteria for throat and sputum culture tests. The results of our study revealed that the rate of postoperative pneumonia was 15.1% in the PO-negative patients, whereas the PO-positive patients had a significantly higher rate of postoperative pneumonia at 35.6%. In the report by Akutsu *et al*. (12), periodontal PO was detected preoperatively in 17.9% of patients, and the reported rate of pneumonia was as high as 71.4% in these patients. Our results showed a weaker association with pneumonia incidence compared to the dental plaque culture test. However, in the present report, when PO were not detected preoperatively, the incidence of postoperative pneumonia was 15.1%, whereas Akutsu *et al*. found a higher incidence of pneumonia at 28.1% in patients with no PO in the dental plaque. This result may indicate that the presence of PO cannot be comprehensively detected by plaque culture alone, or in other words, even if there was no PO detected in dental plaque, some patients may still have PO in the throat or sputum.

On PO examination in the present study, Candida was found to be very common and was detected in 19 of 98 patients (19.4%). Sumi *et al*. (18) examined dental plaque in 138 elderly patients (aged 73.9±9.6 years) and reported that Candida was detected in 63.8%; therefore, the detection rate of Candida in the present study was not considered high.

The consistency of bacteria detected preoperatively and bacteria detected in patients with postoperative pneumonia was 41.7%, which was comparable to the results of Akutsu *et al*. (Akutsu *et al*.: 40%). Those results contradicted the idea that the aspiration of oral PO caused postoperative pneumonia. Potentially pathogenic microorganisms have been detected in the lower respiratory tract in approximately 40% of patients who underwent surgery for lung cancer (19, 20). In patients with inconsistent pre- and postoperative detection of bacteria, the PO in the lower respiratory tract differed from the oral PO before surgery, and these PO multiplied following surgery, which led to the onset of pneumonia. Further studies are needed to clarify this point.

Second, the onset of SIRS early after surgery strongly correlated with postoperative pneumonia, and this tendency was observed more remarkably in PO-positive patients. Multivariate analyses for clinical factors of postoperative pneumonia revealed that SIRS was an independent predictor for pneumonia, and the time of onset of SIRS and pneumonia revealed that in 81% of patients pneumonia developed after postoperative onset of SIRS. In addition, there were significantly more SIRS patients with pneumonia among the PO-positive patients. On the basis of these results, we found that postoperative pneumonia was common among SIRS patients and that this tendency was specifically observed in PO-positive patients.

The onset mechanism of pneumonia may be divided into two steps: 1) the aspiration of bacteria was first required, and 2) the aspired bacteria had to attach to the mucosa of the lower respiratory tract and multiply. This second step could be enhanced by epithelial cell damage, and the multiplication of bacteria may be a major cause of impaired host immunity. A possible reason for the high rate of postoperative pneumonia in PO-positive patients is that the massive production of various cytokines, as a result of SIRS, contributes to the increase in adhesion factors, lung tissue damage, and impaired host immunity. Scannapieco (11) reported that cytokines such as IL-1α, IL-1β, IL-6, IL-8, and tumor necrosis factor (TNF) led to the expression of various adhesion molecules on epithelial cells, thereby facilitating the attachment of bacterial pathogens to the mucosal surface. Also, the hydrolytic enzymes released by activated inflammatory cells impaired the epithelial cells, which consequently facilitated the colonization of respiratory pathogens and the development of pneumonia. Previous studies have described the relationship between cytokines (such as IL-6, IL-8) and lung damage (21, 22). With regards to impaired host immunity, it has been found that anti-inflammatory cytokinemia secondary to SIRS, referred to as compensatory anti-inflammatory response syndrome (CARS), led to immunosuppression (23). These mechanisms were enhanced by SIRS, and in PO-positive patients, SIRS may be more severe because of the higher number of SIRS-positive criteria and the increased duration of SIRS (1).

The reason for a more severe SIRS in PO-positive patients could be due to the priming of certain aspects of the inflammatory response (24, 25). Priming is a transition state in which neutrophils and macrophages become more responsive to activating stimuli, and it is known that exposure to one stimulus enhances the ability of the cell to mount an enhanced activation response to a second individual stimulus (26-30). In the present study, PO-positive patients may be in a state of mild infection because of the fact that preoperative WBC count and serum CRP level were significantly higher. Therefore, a mild infection can set in motion a priming condition, and subsequent surgical stress is capable of causing an exaggerated immune response that results in a more severe SIRS in the PO-positive patients.

Various reports, to date, have described the use of steroids (31), neutrophil elastase inhibitors (32) to prevent various postoperative complications caused by hypercytokinemia.

Steroids were administered to all patients on the day of surgery and also elastase inhibitors were used for two days following surgery. This might have resulted in fewer cases of SIRS on Day 1 following surgery; however, SIRS may not have been adequately controlled. Therefore, this problem needs to be addressed in future studies.

Conclusion

In conclusion, the presence of postoperative SIRS significantly contributed to the onset of pneumonia in PO-positive patients. Thus, this result suggests that preoperative oral care and better control of postoperative SIRS are important to reduce the incidence of postoperative pneumonia. However, the present study was a retrospective study with few subjects, and thus further investigation is required.

Author's Contributions

Conception and design of the study, analysis and interpretation of data, collection and assembly of data, drafting of the article, critical revision of the article for important intellectual content: Shinichi Asaka; Collection and assembly of data: Takeshi Shimakawa, Kentaro Yamaguchi, Takao Katsube, Takebumi Usui, Hajime Yokomizo, Shunichi Shiozawa and Yoshihiko Naritaka; Final approval of the article: Yoshihiko Naritaka.

Conflicts of Interest

The Authors have no conflicts of interest to report.

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