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Risk Factors Associated with Retinal Lesions Resulting from Widespread Systemic Infection

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Purpose: To clarify the prevalence, microbiologic features, and risk factors of endogenous intraocular infections in patients with positive fungal or bacterial blood culture results.

Design: Retrospective case series.

Participants: Inpatients (n = 433) with positive blood culture results who underwent an ophthalmology consultation between January 2006 and September 2012 in Japan.

Methods: We retrospectively reviewed the ophthalmology consultations of 433 inpatients with positive blood culture results. Clinical features of patients with confirmed chorioretinitis or endophthalmitis were analyzed through descriptive statistical methods and univariate and multivariate models.

Main Outcome Measures: Correlation of clinical features with retinal lesions of disseminated bacteremia or fungemia.

Results: Among 433 inpatients with positive blood culture results, 116 (26.8%) were unresponsive and 27 (6.2%) had subjective ocular symptoms. Eighty-four (19.4%) had candidemia, including 16 (3.7%) with retinal lesions. Additionally, 34 patients (7.8%) had chorioretinitis or endophthalmitis in 1 eye (17 patients [3.9%]) or both eyes (17 eyes [3.9%]; 51 eyes total). Of these 34 patients, 20 (58.8%) and 17 (50%) had systemic bacterial and fungal infections, respectively (both infections were noted in 3 patients [8.8%]). *Staphylococcus aureus* was the most common bacteria. *Candida albicans* was the most common fungus, followed by *Candida glabrata*. Catheter-related bloodstream infections were the most common source of infection among the 34 patients with chorioretinitis or endophthalmitis, followed by infective endocarditis, urinary tract infection, and soft-tissue and bone disease. Among the 114 bacteremic patients who underwent an ophthalmology consultation because of suspicion of infective endocarditis, only 16 (14%) had infective endocarditis, of whom only 1 (0.88%) had retinal lesions. Nineteen of 34 patients (55.9%) with retinal lesions survived sepsis. Among them, only 1 patient (5.3%) with bacteremia lost significant vision (no light perception), and the remaining 18 patients (94.7%) regained vision. No patient with candidemia had vision loss. Multivariate analysis revealed that candidemia, infective endocarditis, broad-spectrum antibiotic use, and eye symptoms were independent predictors of retinal lesions (all $P < 0.05$).

Conclusions: An ophthalmology consultation may be useful for patients with candidemia, infective endocarditis, broad-spectrum antibiotic use, or ocular symptoms. However, routine ophthalmologic evaluation may be less efficient for bacteremic patients without definitive infective endocarditis lacking other risk factors. *Ophthalmology Retina 2017;■:1–6 © 2016 by the American Academy of Ophthalmology*

Endogenous ocular infections are rare, but frequently are devastating. These infections are classified as either chorioretinitis or endophthalmitis and occur when pathogens from the bloodstream infiltrate the posterior segment of the eye via the ophthalmic arteries.[1,2] Early diagnosis is essential, but it can be difficult to differentiate between infectious and nonspecific lesions, including cotton-wool spots, white-centered hemorrhages (Roth spots), and exudates, when characteristic chorioretinal lesions are not present or the vitreous is not involved.[3–9]

A retrospective chart review of patients with infectious endogenous endophthalmitis reported that the incidence of bacterial and fungal endogenous endophthalmitis was approximately equal. Overall, *Candida* species are the most common cause of endogenous endophthalmitis, accounting for 34% to 43% of cases.[10–13] Gram-positive organisms are the most frequent cause of bacteremia-associated endogenous endophthalmitis in North America and Europe, with most cases caused by *Staphylococcus aureus*.[4,14] However, the incidence of *Klebsiella pneumoniae* endophthalmitis associated with pyogenic liver abscesses recently has increased, particularly in East Asia.[15,16] In fact, *K. pneumoniae* is now the most common cause of bacteremia-associated endogenous endophthalmitis in East Asia.[17–19] To date, the overall proportion of gram-negative and gram-positive organisms has not changed.[14]

Positive blood culture results have been reported in 74% of patients with endogenous bacterial endophthalmitis.[14] However, studies also have reported a widely varying

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frequency of positive blood culture results ranging between 0% and 69% in patients with *Candida* endophthalmitis.[6,13,19–21] This suggests that the incidence of *Candida*-associated endophthalmitis is somewhat controversial.

Candida endophthalmitis often is treated successfully, but the visual prognosis for patients with endogenous bacterial endophthalmitis is poor and has not improved significantly during the past 5 decades.[14,22] In Japan, positive blood culture results often prompt routine ophthalmologic consultations because of concern for disseminated ocular lesions. In contrast, it has been suggested that routine ophthalmologic consultation for alert and asymptomatic fungemic inpatients may not be an efficient use of clinical resources.[17,23] The purpose of this study was to identify clinical characteristics that may put patients with positive blood culture results at a higher risk for experiencing ocular complications.

Methods

This study was conducted at St. Luke's International Hospital in Tokyo, Japan. The method of data collection was approved by the St. Luke's International Hospital Institutional Review Board. The requirement of informed consent was waived by the institutional review board because this study involved only the retrospective review of electronic medical records. All study conduct adhered to the tenets of the Declaration of Helsinki.

Study Subjects and Data Collection

This retrospective case series included all adult and pediatric inpatients with positive blood culture results at St. Luke's International Hospital who had undergone an ophthalmologic consultation for evaluation of ocular involvement of a bacterial or fungal organism. All consultations took place between January 2006 and September 2012. When a particular patient had multiple positive blood culture results during the same hospitalization, only data obtained from the first positive blood culture results were included in this study. If a particular patient had multiple consult requests concerning the first positive blood culture results and 1 or more subsequent consultations, in some cases performed weeks after positive blood culture results were detected, this information also was included if the findings had changed. All consultation requests were sent to electronic medical charts by the primary inpatient team after blood culture samples had been obtained. In our hospital, at least 2 sets of blood culture samples and 1 set of urine and sputum culture samples are almost always taken from febrile (>38° C) inpatients. These culture examinations are all covered by national insurance. Blood culture samples were obtained during the study period using both aerobic and anaerobic bottles of the BacT/Alert blood culture system (SYSMEX bioMérieux Co, Ltd, Tokyo, Japan). Bacteremia and fungemia were defined as the isolation of any known bacterial or fungal pathogen in the blood culture sample. Although single positive blood culture results may have represented contamination, they were included in this analysis to limit the risk of selection bias. Additionally, only patients who had received a definite diagnosis by Duke criteria were considered to have infective endocarditis.

Standard practice for inpatient ophthalmologic evaluation at our institution includes obtaining a thorough medical and ophthalmic history, measuring intraocular pressure and visual acuity, and performing slit-lamp and dilated monocular indirect ophthalmoscopic examinations. However, for most inpatients in critical condition, only slit-lamp and dilated monocular indirect ophthalmoscopic examinations were performed by ward ophthalmologists. To standardize the reporting of funduscopic findings, we used the criteria proposed by Donahue et al[24] to classify ocular involvement. The term *chorioretinitis* was used when the infectious process remained localized within the chorioretinal layers, producing focal, deep, white infiltrative chorioretinal lesions. The term *endophthalmitis* was used when the infection obviously extended into the vitreous, as indicated by a vitreal abscess or fluff-ball lesions. Fundus lesions were defined as nonspecific for cotton-wool spots, Roth spots, and exudates that were not characteristic of chorioretinal lesions or vitreal involvement. A retinal examination was defined as showing positive results when retinal lesions consistent with chorioretinitis or endophthalmitis were present.[3,17] If no lesions or only nonspecific lesions were found, the examination results were defined as negative. Patients with any other underlying ocular abnormalities (e.g., macular degeneration, dry eye, and cataracts) were included in these analyses, but were considered to have negative examination results. The relationship between septicemia and these other findings was not examined. Patients with nonspecific or positive findings were reexamined and treated as indicated.

Statistical Analyses

We extracted data from medical records, including age, gender, general status (e.g., ability to verbalize symptoms), ocular symptoms, concomitant systemic disease, sources of infection, broad-spectrum antibiotic use before blood culture testing, laboratory data, microbiology results (e.g., type of micro-organisms and the number of culture-positive bottles), and ocular examination findings. We defined piperacillin–tazobactam, fourth-generation cephalosporins, fluoroquinolones, and carbapenems as broad-spectrum antibiotics. Both intravenous and oral antibiotics were included.

We then analyzed these data through descriptive statistical methods and univariate and multivariate models. Correlations between dichotomous risk factors and retinal lesions were examined using chi-square tests and independent sample *t* tests, as appropriate. Eight significant factors in univariate analyses were entered into a multivariate logistic regression model, with outcome as the dependent variable, to determine the most significant independent predictors of disseminated bacterial and fungal retinal lesions. Odds ratios also were calculated, and $P < 0.05$ was considered statistically significant. Calculations were performed using SPSS software for Windows (SPSS, Inc, Chicago, IL).

Results

A total of 2571 inpatients with positive blood culture results were identified initially in an electronic medical records database search. Of these, 1934 (75.2%) did not have a record of an ophthalmology consultation and immediately were excluded. Ophthalmology consultations were requested for 637 of 2571 inpatients (24.8%) with positive blood culture results. Additionally, 143 patients (5.6%) were seen by an ophthalmologist for problems not relevant to this study (e.g., admitting information or follow-up for diabetic retinopathy, glaucoma, dry eye) and were excluded from analyses. An additional 19 patients (0.73%) were seen during a separate, later hospital admission, and 42 patients (1.6%) had no available ophthalmology record or evaluation, although a consultation had been requested. Finally, a total of 433 consultation records that specifically indicated concerns regarding retinal lesions associated with disseminated bacteremia or fungemia were noted. Therefore, 433 inpatients with positive blood culture results ultimately were included in study analyses (Fig 1).

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