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Original article

Study of ocular candidiasis during nine-year period

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ABSTRACT

Background: To determine the clinical features, fungal profiles, treatment outcomes, and factors that are significantly associated with the visual outcomes of eyes with endogenous fungal endophthalmitis (EFE).
Material and methods: The medical records of 17 eyes of 9 patients diagnosed with EFE during January 2005 to December 2013 were reviewed. The collected data included patient characteristics, visual acuities (VAs), length between appearance of the first sign of infection and the first ophthalmic examinations, fungal profiles, and treatment regimen. The main outcome measure was the VA. Statistical analyses were done to detect the factors significantly associated with the visual prognosis.
Results: The median age at presentation was 67 years. Seven patients had *Candida albicans*, and 2 had *Candida tropicalis*. Eight patients received intravenous fosfluconazole, 4 systemic micafungin, 4 oral itraconazole, and 2 intravenous voriconazole. The minimum inhibitory concentrations of fluconazole against *Candida albicans* isolated from 5 patients ranged from 0.25 to 1.0 μg/mL. A final VA of ≥20/200 was achieved in 69.2% of the eyes. Multiple regression analysis ($r^2 = 0.695$) detected both initial logMAR (the Logarithm of the minimum angle of resolution) VA ($P = 0.0067$) and longer length between onset of symptoms and the first ophthalmic examinations ($P = 0.0491$) as significant worsen factors for final logMAR VA.
Conclusions: Early ophthalmic consultation, better initial visual acuity, and use of effective systemic antifungal treatment might lead to relatively good visual outcomes in EFE.

1. Introduction

Endogenous fungal endophthalmitis (EFE) is a serious intraocular inflammatory disorder that typically occurs in compromised host. The incidence of EFE has increased since the late 1980s [1,2], and *Candida* spp. are the most commonly isolated pathogens in these eyes. Among the *Candida* spp., *C. albicans* is the most commonly isolated species [1,3–7]. According to the guidelines of Infectious Diseases and Society of America (IDSA) for candidiasis infections, and the guidelines for the Management of Deep-seated Mycoses in Japan (2007), most patients with risks of ocular candidiasis are referred to an ophthalmologist at an early stage, and systemic antifungal agents are instituted [8]. The incidence of candidosis has been greatly reduced [9]. However, the rate of ocular candidiasis is approximately 20% in patients with candidemia, and there are still cases with poor visual outcomes [3,4,10–13]. Although most patients with candidemia are already on systemic antifungal medications at the time of an examination by an ophthalmologist [5,10], it is unclear which factors are related to the prognosis and what treatment strategy ophthalmologists should plan to improve the prognosis.

The purpose of this study was to investigate the clinical features, microbiological spectrum, and treatment outcomes of eyes with EFE in both inpatients of our hospital and outpatients consulted from other hospitals. The treatments in the current study were consistent with the Guidelines for Management Deep-seated Mycoses 2014 in Japan, and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guideline [14], as a result. To accomplish this, we reviewed the medical records of all patients with EFE treated in our institution during a 9-year period.

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2. Material and methods

2.1. Patients

The study protocol was approved by the Institutional Review Board of Gifu University Graduate School of Medicine. We reviewed the medical records of 9 consecutive patients who were diagnosed with EFE between January 2005 and December 2013. All of the patients were referred to Department of Ophthalmology, Gifu University Graduate School of Medicine. The patients were diagnosed with EFE caused by candidemia which was defined by at least one positive blood culture for *Candida* spp., and the clinical signs of fever, hypotension, tachypnea [10], and/or vitreoretinal findings.

For the classification of ocular candidiasis, we used the criteria proposed by previous studies [1,4,7,10]. An eye was diagnosed with proven endophthalmitis when it was caused by ocular candidiasis with positive cultures of the vitreous humor. An eye with a fungal mass penetrating through the inner limiting membrane and budding in the vitreous cavity was diagnosed as probable endophthalmitis. An eye with deep, focal, fluffy white lesions located within the chorioretinal layers was diagnosed as probable chorioretinitis. If signs of chorioretinitis were observed in patients with an underlying disease, *e.g.* diabetes, hypertension, or concomitant bacteremia, these cases were classified as possible chorioretinitis [4,10].

The medical records of all the patients were reviewed. The data collected from the medical records included the age, sex, laterality, presenting complaints, underlying systemic infections, level of β-D-glucan, history of indwelling catheters, cultured fungal species, length between appearance of the first sign of infection and the first examination by an ophthalmologist at our hospital or other hospital, time from positive culture results to ophthalmic consultation, antifungal agents at time of consultation, any changes in the management from ophthalmic consultation, vitreoretinal findings, treatment methods, and initial and final best-corrected visual acuity (BCVA). The main outcome measure was the BCVA. In earlier reports [15,16], a BCVA of counting fingers (CF) or better was classified as being a good visual outcome for the statistical analyses, however we used 20/200 or better as a good visual outcome. Other outcome measures included the results of microbiological investigations and anatomical and clinical outcomes.

2.2. Statistical analyses

When data of the current study was analyzed statistically, the right eye and the left eye in one patient were considered to be independent. The decimal BCVA values were converted to the logarithm of the minimum angle of resolution (logMAR) units. The following arbitrary logMAR values were used; CF = 2.00 logMAR units, hand motion = 2.30 logMAR units, light perception = 2.60 logMAR units, and no light perception = 2.90 logMAR units [17,18]. To detect the clinical factors associated with the BCVA, single logistic regression and single regression analysis were used firstly. Logistic regression was used employing initial or final VA of ≥20/200 as the outcome value. Regression analysis was used employing initial or final logMAR VA as the outcome value and other continuous values as explanatory variables. When single logistic regression or single regression analysis detects several factors significantly related to BCVA, multiple logistic regression or multiple regression analyses were used to detect the final association with BCVA, including all factors detected by single logistic regression or single regression analysis. Fisher's exact test, Mann–Whitney U test, and Spearman's rank correlation coefficient were also used to determine the statistical significances. The odds ratio and partial regression coefficient were calculated, and the 95th percentile confidence intervals (95%CI) were determined. A P value < 0.05 was considered to be significant. All statistical analyses were performed using SPSS software version 16.0 (SPSS Japan, Tokyo, Japan).

3. Results

3.1. Patient characteristics and systemic features

The characteristics and systemic features of the 17 eyes of 9 Japanese patients are shown in Tables 1 and 2. The median age at presentation was 67.0 years with a range of 25–78 years (Table 2). There were 6 (66.7%) men and 3 (33.3%) women, and 4 (44.4%) were inpatients at our hospital and 5 (55.6%) were outpatients consulted from other hospitals. In the current study, outpatients mean patients who were consulted for ophthalmic examinations from other hospital. The median follow-up period was 20.1 months with a range of 1.2–70.0 months.

All patients had one or more risk factors for EFE; 5 patients had gastrointestinal tract surgery and 1 patient had orthopedic surgery. Two patients had diabetes mellitus, 1 had renal failure, 1 had the myelodysplastic syndrome, and 2 had pneumonia (Table 2). Systemic steroids were being used to treat the underlying illness in 3 patients. Eight patients (88.9%) had indwelling catheters, and none of the patients had neutropenia of 500/mL or less.

The most common initial systemic symptom was fever in 4 (44.4%) patients and all of whom were inpatients. They ran fevers within 10 days before ophthalmic examination (median 7.5 days; range, 5–10 days) and were referred to us within 5 days (median 3 days; range, <1 to 5 days) following the detection of positive blood cultures and no ocular symptoms. On the other hand, among the outpatients consulted from other hospitals, the median days between appearance of the first sign of infection and the day of the first ophthalmic examination at regardless of a hospital were 20 days with a range of 8–34 days. There was a significant delay in outpatients comparing the inpatient in the length from appearance of the first sign of infection to the first ophthalmic examination at regardless of a hospital (median 20 vs. 7.5 days, $P = 0.0036$; Mann–Whitney U test). Among the outpatients consulted from other hospital, the day from appearance of the first sign of infection to ophthalmic consultation to our hospital was further longer (median 22 days; range, 9–66 days).

At the first visit to our institution, the plasma level of β-D-glucan was measured byβ-D- Glucan test Wako (Waco Pure Chemical Industries, Osaka, Japan) in all patients and it's range was between 21 and 2462 pg/mL. Thus, it was positive in all patients for a cut-off value of 10 pg/mL [19].

3.2. Ocular features

The EFE was unilateral (right) in 1 patient and bilateral in 8 patients (Tables 1 and 2). Four (44.4%) patients had no ocular symptom, 2 (22.2%) had floaters, and 3 (33.3%) had blurred or decreased vision. All of the 5 patients who had these ocular symptoms were outpatients consulted form other hospitals. A correct initial ocular diagnosis of EFE was made by an ophthalmologist at other hospital in 3 patients. Other initial ocular diagnoses were uveitis (n = 1) and vitreous hemorrhage (n = 1).

For the classification, 4 (23.5%) eyes were diagnosed with proven endophthalmitis, 1 (5.9%) eye was probable endophthalmitis, 12 (70.6%) eyes were probable chorioretinitis, and no eye was possible chorioretinitis (Table 2). There was a significant difference between endophthalmits and chorioretinitis in the length from appearance of the first sign of infection to the first ophthalmic examinations at