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Prognosis of Endogenous Fungal Endophthalmitis and Utility of Ishibashi's Classification

Yukihiro Sato, Shinobu Miyasaka and Hiroyuki Shimada

Department of Ophthalmology, Nihon University School of Medicine, Tokyo, Japan

Purpose: Evaluations of visual acuity outcomes of eyes with endogenous fungal endophthalmitis were made retrospectively, according to the classification proposed by Ishibashi.

Methods: We surveyed endogenous fungal endophthalmitis cases at the 4 Nihon University Hospitals and 20 affiliated hospitals. Sixty eyes of 34 patients were classified into five stages according to Ishibashi's system, and therapeutic methods and visual outcomes in each stage were then evaluated.

Results: Systemic antifungal drugs were efficacious in 82% of stage II and 69% of stage IIIa cases. Antifungal drugs were even efficacious in 42% of stage IIIb cases. Among the unresponsive cases, only half had been given the maximal dosage of antifungal drugs. Half of the eyes in which vitrectomy had been performed at stage IIIb achieved a postoperative visual acuity of 0.5 or better and none had a visual acuity of less than 0.03.

Conclusion: Based on the above results, we concluded that systemic antifungal drugs should be administered at the maximal dosage to stage II and IIIa cases. If these eyes progress to stage IIIb despite receiving the maximal dosage, vitrectomy is indicated. For stage IIIb eyes, the maximal dosage should be administered first. If not efficacious, vitrectomy should be carried out before progression to stage IV. **Jpn J Ophthalmol 2001;45:181–186** © 2001 Japanese Ophthalmological Society

Key Words: Antifungal drugs, endogenous fungal endophthalmitis, Ishibashi's classification, vitrectomy.

Introduction

Endogenous fungal endophthalmitis is reportedly a relatively rare disease. However, since 1984, the number of patients with this disease has increased rapidly in Japan, with the massive dose administration of antibiotics or anticancer agents and the common use of intravenous hyperalimentation (IVH).[1,2]

In 1993, Ishibashi[3] proposed a new classification for staging of this disease (Ishibashi's classification, Table 1), aimed at facilitating treatment selection for endogenous fungal endophthalmitis.

However, no previous studies have examined the usefulness of this staging method in a large number of patients. We conducted a survey of this disease in the 4 Nihon University School of Medicine Hospitals and 20 affiliated hospitals and report our findings herein.

Materials and Methods

We conducted a questionnaire survey to determine whether there were patients with endogenous fungal endophthalmitis, and their clinical features, treatment and clinical course, in the 4 Nihon University Hospitals and 20 affiliated hospitals, where surgery for systemic malignant tumors had been performed, between January 1994 and December 1998. Questionnaires were collected from all institutions. In 11 (46%) of the 24 hospitals, there were patients who had been diagnosed as having endogenous fungal endophthalmitis during the above period. In 34 patients (60 eyes) with this disease, background factors, such as underlying systemic disease, were examined, and the stage was evaluated according to Ishibashi's classification. Treatments and the usefulness of the classification system were retrospectively evaluated.

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Correspondence and reprint requests to: Yukihiro SATO, MD, Department of Ophthalmology, Surugadai Hospital of Nihon University, 1-8-13 Surugadai, Kanda, Chiyoda-ku, Tokyo 101-8309, Japan

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Table 1. Ishibashi's Proposed Classification of Stages of Endogenous Fungal Endophthalmitis

Stage I: Appearance of inflammatory cells in anterior chamber and vitreous
State II: Appearance of white round lesions in posterior fundus
Stage IIIa: Appearance of mild opacity in vitreous
Stage IIIb: Moderate or severe opacity in vitreous
Stage IV: Retinal detachment or totally opaque vitreous

Results

Patient Backgrounds

Thirty-four patients (25 men and 9 women; 60 eyes). Age at diagnosis ranged from 10 to 82 years (mean = 60.2 ± 13.6 years). Eight patients (8 eyes) had monocular, while 26 patients (52 eyes) had binocular endogenous fungal endophthalmitis.

Underlying Systemic Diseases

Twenty (59%) of 34 patients developed endogenous fungal endophthalmitis after surgery for systemic malignant tumors. Three patients (9%) developed the disease after ileus surgery. Two patients (6%) had gastric ulcer. Nine patients (26%) had other diseases. Malignant tumors consisted of gastric cancer in 7 patients, large intestinal cancer in 7, esophageal cancer in 2, bladder cancer in 2, renal cancer in 1, and ovarian cancer in 1. Other underlying systemic diseases included gastric perforation, hemorrhagic gastritis, cholecystitis, hepatic coma, multiple myeloma, pleuritis, multiple trauma, enterocleisis and anorexia in one patient each. Six patients had diabetes.

Systemic Agents

Antibiotics had been prescribed for 29 (85%) of the 34 patients. Anticancer agents had been prescribed for 7 patients (21%), adrenocorticosteroids for 4 (12%), and immunosuppressive agents for 3 (9%) (some had more than one condition). There were only 2 patients (6%) who had not received any of the above drugs.

Incidence of IVH and Fever

Twenty-eight patients (82%) had received IVH; 26 (76%) had experienced fever (39°C or higher).

Confirmation of Fungus

In 25 patients (74%), fungus was detected by specific methods. *Candida albicans* was identified in all patients. Fungus was detected at the end of the IVH catheter in 12 patients, by arterial blood culture in 7, by urine culture in 2, in blood (1→3) beta-D-glucan in 2, in sputum in 1, and in venous blood in 1 (fungus was detected by more than one method in some patients). In 7 patients, fungus was locally detected by microscopy or culture using vitreal specimens collected during vitrectomy.

Ishibashi's Classification at Diagnosis

At diagnosis, 2 (3%), 21 (35%), 18 (30%), 16 (27%), and 3 eyes (5%) were evaluated as being at stage I, II, IIIa, IIIb, and IV respectively, according to Ishibashi's classification (Table 2). Thirty-four eyes (57%) in total were evaluated as being at stage III.

Ophthalmological Treatment and Prognosis

In 47 eyes, ophthalmological treatment and prognosis could be confirmed (Table 3). Of 47 eyes, 1, 17, 13, 14, and 2 were evaluated as being at stage I, II, IIIa, IIIb and IV, respectively.

In this study, visual acuity was used as an outcome parameter, and mainly classified into less than 0.03 and 0.5 or better. This was because severe visual loss was defined as 5/200 or worse acuity in the Endophthalmitis Vitrectomy Study, which was conducted in the United States[4], and because visual acuity of 0.5 or better was considered to be adequate for reading.

Furthermore, patients in whom lesions disappeared or were reduced and there was no recrudescence after discontinuation of drug administration were regarded as "responded or efficacious" (ie, responders to antifungal agents).

One stage I eye responded to systemic administration of an antifungal agent, and final visual acuity was 1.2. In this patient, the contralateral eye was evaluated as stage IV.

Of 17 stage II eyes, 14 responded to antifungal agents. The final visual acuity was less than 0.03 in 7% and 0.5 or better in 86% of these eyes. Visual acuity less than 0.03 was associated with cicatrization at the macula. The remaining 3 eyes did not respond to antifungal agents, and deteriorated to stage IV.

Table 2. Ishibashi's Classification Applied in This Study for Diagnosis

Stage I: 2 eyes (3%)
Stage II: 21 eyes (35%)
Stage IIIa: 18 eyes (30%)
Stage IIIb: 16 eyes (27%)
Stage IV: 3 eyes (5%)

Table 3. Ophthalmological Treatment and Prognosis in 47 Eyes

	No. of eyes	% < 0.03	% ≥ 0.5
A. State I (1 eye)			
Responded to antifungal agent	1	0	100
No response to antifungal agent	0		
B. Stage II (17 eyes)			
Responded to antifungal agent	14	7	86
No response to antifungal agent	3	100	0
C. Stage IIIa (13 eyes)			
Responded to antifungal agent	9	11	67
No response to antifungal agent	4	0	50
D. Stage IIIb (14 eyes)			
Responded to antifungal agent	5	0	100
No response to antifungal agent	7	43	29
Vitrectomy without antifungal agent*	2	0	50
E. Stage IV (2 eyes)			
Responded to antifungal agent	0		
No response to antifungal agent	1	100	0
Vitrectomy without antifungal agent*	1	100	0
F. Stages I to IV (47 eyes)			
Responded to antifungal agent	29	7	83
No response to antifungal agent	15	47	27
Vitrectomy without antifungal agent*	3	33	33

*Vitrectomy was performed immediately after diagnosis without administration of antifungal agents.

Vitrectomy was not performed due to the poor general condition of the patients. These patients had visual acuity of hand motion or worse.

Of 13 stage IIIa eyes, 9 responded to antifungal agents. The final visual acuity was less than 0.03 in 11% and 0.5 or better in 67% of these eyes. Visual acuity less than 0.03 was associated with cicatrization at the macula. The remaining 4 eyes did not respond to antifungal agents, and deteriorated to stage IIIb. Vitrectomy was performed in these 4 eyes. None of the 4 had a visual acuity worse than 0.03 and 2 (50%) had better than 0.5 acuity.

Of 14 stage IIIb eyes, 12 were administered antifungal agents. Five eyes responded to this treatment, while 7 did not. In 2 eyes, vitrectomy was immediately performed without administration of antifungal agents. In all 5 eyes that responded to antifungal agents, final visual acuity was 0.5 or better. However, final visual acuity was less than 0.03 and 0.5 or better in 43% and 29%, respectively, of the 7 eyes that did not respond to antifungal agents. Briefly, in 4 of these 7 eyes, vitrectomy was performed at stage IIIb. None of the eyes had a visual acuity below 0.03, and in half, visual acuity was 0.5 or better. In 1 eye, vitrectomy was performed after deterioration to stage IV, resulting in a visual acuity of only hand motion. In the remaining 2 eyes, administration of antifungal agents alone was continued due to the poor general condition of the patients, despite deterioration to stage IV. Visual acuity was only light perception in these 2 cases. Furthermore, in the 2 eyes in which vitrectomy was immediately performed without antifungal agents, final visual acuity was 0.09 and 1.0.

Of 2 stage IV eyes, loss of sight occurred in 1 in which vitrectomy was immediately performed. In the eye in which an antifungal agent alone was administered due to the patient's poor general condition, final visual acuity was light perception.

Visual acuity outcomes are summarized in Table 3F. Twenty-nine eyes that responded to antifungal agents showed good outcomes. Seven percent of the eyes had a visual acuity worse than 0.03, while 83% had an acuity of 0.5 or better. On the other hand, in 47% of 15 eyes that did not respond to antifungal agents, final visual acuity was less than 0.03. In 27% of these 15 eyes, final visual acuity was 0.5 or better. However, among eyes that did not respond to antifungal agents, none of 4 eyes in which vitrectomy had been performed due to progression from stage IIIa at diagnosis to stage IIIb had a final visual acuity below 0.03. Also, none of the 4 eyes in which the stage was evaluated as IIIb at diagnosis, and in which surgery had been performed in stage IIIb, had an acuity of worse than 0.03. Two of the latter 4 eyes had a postoperative visual acuity of 0.5 or better. Furthermore, of the 3 eyes in which vitrectomy had

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been performed without administration of antifungal agents, one had a visual acuity below 0.03, while one had a visual acuity above 0.5.

Types of Antifungal Agents and Efficacy

Responses to systemic administration of antifungal agents are shown in Table 4. Of 44 eyes, 29 (66%) responded to this treatment, while 15 eyes (34%) did not. However, of the 15 eyes, maximal doses of antifungal agents were prescribed in one stage II eye, 2 stage IIIa eyes, and 4 stage IIIb eyes (total: 7 eyes).

"Maximal dose administration" indicates administration of "the maximal daily dose," as recommended by the manufacturer of each agent, for 2 weeks or more. The period of 2 weeks or more was established, because Someya et al[5] reported fundus lesions in 4 patients treated with itraconazole to be improved more than 2 weeks after the initiation of treatment, and that drug administration achieved a complete cure in 1 of these patients.

The maximal daily doses of frequently prescribed agents are as follows: fluconazole, 400 mg; miconazole, 1,200 mg; and itraconazole, 200 mg.

When the effects of antifungal agents were examined with respect to the stages of Ishibashi's classification, response rates were 100%, 82%, 69%, 42%, and 0% in stage I, stage II, stage IIIa, stage IIIb, and stage IV eyes, respectively.

The antifungal agents are summarized in Table 5. Twenty-four eyes (55%) were treated with fluconazole alone. Four eyes (9%) were treated with miconazole alone. Two eyes (6%) were treated with amphotericin B syrup alone (a 10-year-old child).

In 11 cases (24%), fluconazole was switched to itraconazole. In one case (2%), fluconazole was switched to miconazole. In one case (2%), itraconazole alone was switched to combination therapy with itraconazole and fluconazole. In one case (2%), fluconazole was switched to miconazole, and then changed to itraconazole.

As the dose and administration period varied, response rates were examined only for frequently prescribed agents. Response rates were 63% in eyes treated with fluconazole alone and 82% in those in which fluconazole was replaced by itraconazole.

Table 4. The Response to Systemic Administration of Antifungal Agents in 44 Eyes*

Stage	Responded†	No response‡
I	1/1 eyes (100)	0/1 eyes (0)
II	14/17 eyes (82)	3/17 eyes (18)
IIIa	9/13 eyes (69)	4/13 eyes (31)
IIIb	5/12 eyes (42)	7/12 eyes (58)
IV	0/1 eyes (0)	1/1 eyes (100)
Total	29/44 eyes (66)	15/44 eyes (34)

*Values in parentheses are percentages.
†Responded to antifungal agent.
‡No response to antifungal agent.

Table 5. Antifungal Agents*

Antifungal Agent	No. of Eyes
Fluconazole alone	24 eyes (55)
Miconazole alone	4 eyes (9)
Amphotericin B syrup alone	2 eyes (6)
Fluconazole → Itraconazole	11 eyes (24)
Fluconazole → Miconazole	1 eye (2)
Itraconazole → Itraconazole + Fluconazole	1 eye (2)
Fluconazole → Miconazole → Itraconazole	1 eye (2)

*Values in parentheses are percentages.

Outcome After Vitrectomy

In 9 eyes in which vitrectomy was performed because there was no response to antifungal agents and in 3 eyes in which vitrectomy was performed without administration of antifungal agents (total: 12 eyes), the visual acuity outcome was examined (Table 6). None of 10 eyes in which surgery was performed at stage IIIb had a final visual acuity below 0.03. Five (50%) of these eyes had an acuity of 0.5 or better. Of the 2 eyes in which surgery was performed at stage IV, loss of sight occurred in one and visual acuity was hand motion in the other.

Discussion

In the first part of this report, background factors are discussed. In patients with endogenous fungal endophthalmitis, medical histories are characterized by (1) the presence of severe underlying diseases, such as cancer, hematological disorders, and recuperation from major surgery; (2) long-term massive dose administration of anticancer agents, immunosuppressive agents, antibiotics, and steroids; (3) IVH

Table 6. Outcome After Vitrectomy in 13 Eyes*

	Visual Acuity	
Stage	<0.03	≥0.5
IIIb	0/10 eyes (0)	5/10 eyes (50)
IV	2/2 eyes (100)	0/0 eyes (0)

*Values in parentheses are percentages.

and intravenous indwelling catheters; and (4) hematomycosis.[1] In this survey, a history of IVH and fever of 39°C or higher suggesting the presence of hematomycosis were confirmed in approximately 80% of patients. Approximately 60% of the patients developed endogenous fungal endophthalmitis after surgery for malignant tumors. However, there were a few patients without serious underlying diseases (2 patients with gastric ulcer, 1 with anorexia). One of the gastric ulcer patients was previously reported by the Department of Internal Medicine, Surugadai Nihon University Hospital.[6] In this patient, IVH was performed because the fasting period had been prolonged. With respect to systemic administration, the agents described above (2), including particularly antibiotics, had been prescribed in most cases. However, 2 patients had not been given any of these agents. One had a gastric ulcer, the other anorexia. These 2 patients had received IVH. These cases suggest that endogenous fungal endophthalmitis may develop in patients undergoing IVH even in the absence of serious underlying diseases.

In this survey, the stage at diagnosis was evaluated as I, II, IIIa, IIIb, and IV in 3%, 35%, 30%, 27%, and 5%, respectively, of the eyes according to Ishibashi's classification. There were only 2 stage I eyes. In these patients, the contralateral eyes were in stages IIIb and IV, respectively. There were no stage I eyes with normal contralateral eyes. The patient with gastric ulcer, who was reported by the Department of Internal Medicine[6], initially consulted the Department of Ophthalmology for conjunctival congestion of the left eye and a disagreeable ocular sensation. At this point, findings corresponding to stage I were observed in the left eye. However, episcleritis was diagnosed on the initial consultation with our department, suggesting that it is difficult to diagnose stage I endogenous fungal endophthalmitis.

This section of the report focuses on therapeutic strategies, with respect to the stages of Ishibashi's classification. When the effects of antifungal agents were examined, response rates were 100%, approximately 80%, approximately 70%, approximately 40%, and 0% in stage I, stage II, stage IIIa, stage IIIb, and stage IV eyes, respectively. Less than 10% of responders showed severe visual loss (visual acuity: less than 0.03). Approximately 80% of responders had a visual acuity of 0.5 or better, adequate for reading. Two eyes had visual acuities below 0.03 due to cicatrization on the macula. However, such events were observed only in 2 (7%) of 29 eyes that responded to antifungal agents. Overall, the visual acuity outcome was good in responders.

Management of nonresponders to antifungal agents may be an issue. In our survey, 15 eyes did not respond to antifungal agents. As described above, about half the eyes did not respond despite administration of the maximal dose of antifungal agents. In about half of the nonresponders, final visual acuity was less than 0.03. In less than 30% of nonresponders, final visual acuity was 0.5 or better. However, among nonresponders, none of the eyes in which vitrectomy had been performed in stage IIIb had a visual acuity below 0.03. Half of these eyes had a final visual acuity better than 0.5. In eyes with deterioration to stage IV or eyes in which the stage was evaluated as IV at diagnosis, final visual acuity was no better than hand motion, regardless of whether surgery had been carried out. This result was similar to the outcomes of vitrectomy. None of the eyes in which vitrectomy had been performed in stage IIIb had a visual acuity below 0.03. Half of these eyes had a final visual acuity of 0.5 or better. However, in eyes in which surgery had been performed in stage IV, final visual acuity was hand motion or worse. Thus, the stages of Ishibashi's classification accurately reflect the effects of antifungal agents and outcome after vitrectomy, and may be useful for selecting a therapeutic strategy.

In the article proposing this staging system,[3] Ishibashi indicated that a complete cure was achieved by systemic administration of antifungal agents alone in 36 of 40 eyes with stage IIIa or lower disease classification (20 patients). In our survey, about 20% of stage II eyes and about 30% of stage IIIa eyes did not respond to antifungal agents. Ishibashi did not describe the antifungal treatment in detail,[3] and the reason for the difference in treatment results between the two studies is unclear.

However, among the eyes of nonresponders in our survey, only about 50% had been given the maximal dose of antifungal agents. We cannot rule out the possibility that the number of nonresponders might have been lower if the maximal dose had been administered.

Although the prognosis of eyes which deteriorated to stage IV was very poor, the clinical course of endogenous fungal endophthalmitis is relatively slow compared with that of bacterial endophthalmitis. Furthermore, the possibility of observing the fundus allows careful follow up after administration of the maximal dose of antifungal agents in stage IIIb eyes. Thus, it may be possible to treat stage IIIb eyes with the maximal dose of antifungal agents prior to vitrectomy. If signs such as increased vitreous opacity, which indicate deterioration to stage IV are ob-

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served, vitrectomy should be performed as soon as possible.

Based on these results, we consider the following therapeutic strategies to be appropriate: (1) in patients with endogenous fungal endophthalmitis, Ishibashi's classification should be applied; (2) in stage II and stage IIIa patients, the maximal dose of antifungal agents should be administered, but when the condition deteriorates to stage IIIb, vitrectomy should be performed; and (3) In stage IIIb patients, the maximal dose of antifungal agents should initially be administered, and in nonresponders, vitrectomy should be performed before the condition deteriorates to stage IV.

In the future, long-term outcomes should be examined in patients treated using these strategies. Furthermore, in this survey, administration of the maximal daily dose, as indicated by the manufacturer, for 2 weeks or more was regarded as "maximal dose administration." However, the period of 2 weeks or more was based only on the course described in the literature cited above.[5] The most appropriate administration period at the maximal daily dose should be further examined in the future.

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