Jpn. J. Infect. Dis., 60, 33-39, 2007

Original Article

Histopathological Study on Experimental Endophthalmitis Induced by Bloodstream Infection with *Candida albicans*

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(Received October 16, 2006. Accepted November 27, 2006)

SUMMARY: To investigate the details of the pathophysiology of endogenous fungal endophthalmitis (EFE), we performed sequential histological and ophthalmoscopic examination on a rabbit model comparing immunocompromised EFE developed using a steroid with an immunocompetent one intravenously inoculated with *Candida albicans*. The ophthalmoscopic examination and histological analysis of the retina in both groups demonstrated that lesions appear on the equator of the eyeball and then spread toward the posterior pole. It has been speculated that, because of the unique innate vasculature system of the equator, there is a sudden, decrease of shear stress in rheologically, resulting in adhesion of yeast cells to the endothelial cells. Histological examination revealed that the degree of polymorphonuclear leukocyte (PMN) infiltration was equivalent in the two groups. However, the appearance of PMN was delayed and the number of fungi was higher in the state of hyphae and/or pseudohyphae in the steroid-treated group. Furthermore, the eyeball was found to be the second earliest organ involved in candidemia. Our results indicate that ophthalmic examination is useful to monitor the development and systemic involvement of endophthalmitis in patients with candidemia.

INTRODUCTION

Endogenous fungal endophthalmitis (EFE) has become one of the most serious problems in contemporary medicine due to the increasing number of immunocompromised patients. The incidence of EFE in patients with *Candida* septicemia has been reported as 10 to 45% (1-4). *Candida albicans* is the most common pathogen causing EFE, being isolated in 85-99% of all cases (4-7). Candidemia occurs in patients treated with multiple antibiotics, systemic steroids, and immunosuppressives and also in those subjected to abdominal surgery or implanted with long-standing intravenous catheters. These patients are known to experience an impairment of host defense mechanisms (8-11). However, EFE is difficult to detect at an early clinical stage, because most patients do not complain of visual disturbance due to the severity of their underlying diseases. In addition, the eye symptoms usually do not appear until the primary focus, initially limited to part of the retina, extends to involve the macula and/or ruptures into the vitreous body.

In patients with EFE, fungi, usually pathogenic yeasts, may disseminate and spread via the bloodstream, and settle in the choroid. Infection of the choroid has been regarded as the initial event leading to endophthalmitis (12-15). Many experiments have been performed on animal models of EFE, but there have been no studies on immunocompromised EFE. A few studies have been done on the pathophysiology, ophthalmoscopic findings, and histology of retinal lesions (12-20). Although EFE has been recognized as a clinical manifestation of a generalized infection (10), the relationship between a generalized infection and endophthalmitis, in magnitude and/or under immunocompromised conditions, has not been clarified. In this study, we describe a model of immunocompromised EFE developed using steroid, and compare it to an immunocompetent one. In addition, we performed histological and sequential ophthalmoscopic examinations to clarify the pathomechanism of endophthalmitis and the correlation with fungemia in a rabbit model of endogenous *Candida* endophthalmitis.

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MATERIALS AND METHODS

Microorganism: The J-GO strain of *C. albicans*, TIMM0239, which was maintained at the Teikyo Institute of Medical Mycology, Tokyo, was employed in this study.

Animals: Sixty-six male Japanese white rabbits (JW-NIBS/Y), weighing 1.8 to 2.0 kg (Sankyo Laboratory Service Co., Tokyo, Japan) were used because of the relatively large size of their eyes and arteries. Microscopy and a fundus camera usually employed in clinical practice were used to observe the retinal lesions.

Infection: *C. albicans* was prepared from frozen isolates that were subcultured onto yeast peptone glucose (YPG) agar slants. These slants were kept at 34°C for 24 h. The yeast was collected and suspended in saline solution at a cell density of 2×10^7 cells/mL. Each animal was inoculated with 0.5 mL of the yeast suspension via the right auricular vein. That is, each rabbit was intravenously infected with 5×10^6 cells of *C. albicans*. The size of the inoculum was chosen on the basis of preliminary experiments that resulted in a mortality rate of 98% in a week.

Experiment: The rabbits were divided into two experimental groups, one of which was treated with steroid (Mitaka Pharmaceutics Co., Ltd., Tokyo, Japan). The drug was administered subcutaneously at a dose of 3 mg/kg of body weight on the -1st, 2nd, 5th, and 8th day of the experiment, to cause immunosuppression and thereby facilitate establishment of infection.

Histopathological examination: After the infection, the

ocular fundus was observed and digitally photographed each day. Rabbits were sacrificed on the 1st, 3rd, 5th, 7th, 10th, and 14th day after the inoculation, and their eyes, brain, heart, lungs, liver, spleen, adrenals, and kidneys were removed for histopathological examination. These organs were fixed in 4% buffer formalin and paraffin sections were prepared in the routine fashion. For the morphometric analysis, the eyeball was cut along the largest sagittal plane after fixation and then the number of foci were counted, measure the area themselves, and the distance from the optic disc was determined by stereomicroscopic observation with digital imaging.

For histological examination, the eyeball was cut along the equator line and a digital image was recorded. After this, the specimen was cut into bands of 5 mm in width, and paraffin sections were also prepared in the routine fashion. These sections were stained with hematoxylin and eosin (H&E) stain and periodic acid Schiff's (PAS) stain for light microscopic observation.

Statistical analysis: Mann-Whitney's U test was used for the statistical analyses to determine the significance of differences in the foci area and distance from the optic disc. Dispersion of data was analyzed by F test. Values of $P < 0.05$ were considered to indicate statistical significance.

RESULTS

Serial evaluation of the ocular fundus: No significant changes were found until the 2nd day after inoculation in both experimental groups. On the 3rd day, the ophthalmoscopic examination revealed the first lesions in rabbits of both groups (Fig. 1), under the retina and among the choroidal vessels. The number of lesions was smaller in the non-treated group than in the steroid-treated group. The lesions appeared as a light white and round-shaped spot with a pale halo, of approximately half the area of the optic disc. After establishment of the initial lesion, the lesions increased in number and became gradually larger, with the borders becoming clear and protruding into vitreous (Fig. 2). In the non-treated group, the lesions decreased in size and number after the 10th day (Table 1). On the other hand, in the steroid-treated group, a continuous increase in size and number was observed until the 10th day after infection. Since most of the rabbits treated with the steroid died after the 10th day, no ophthalmoscopic examination was performed in this group.

The results showed that the lesions were larger in size and number in the steroid-treated group. In addition, the retinas without lesions were more pale in appearance. The differences in ophthalmoscopic findings on the 7th day are summarized in Table 2.

Morphometric analysis of retinal lesions: The first lesion developed in the retina on the 3rd day after inoculation, but the lesion was too small to be observed by stereomicroscopy. Therefore, the eyeballs from rabbits of both experimental groups obtained on the 5th and 7th day after infection were employed for morphometric analysis.

On the 5th day after infection, significant differences were found in the average number and mean area of lesions between the two groups (4.67 ± 2.58, versus 8.33 ± 3.20, and 0.49 ± 0.27 mm^2 versus 0.99 ± 0.52 mm^2, respectively). The difference in unevenness of area of each lesion indicated as the standard deviation was also significant. On the other hand, there was no significant difference in the distance between lesions and the optic disc, which was 9.39 ± 2.83 mm and 8.96 ± 4.21 mm, respectively. On the 7th day after infection, significant differences were also found in the average number and mean area, but not in the distance between lesions and the optic disc (Fig. 3 and Table 3). Accordingly, on both the 5th and 7th day, significant differences were found in number, mean area, and unevenness of the area of lesions which were generally prominent in the steroid-treated group. There was no difference in the distance between lesions and the optic disc.

Histopathological examination: 1. Histological findings of the retinal lesions: 1-1. Non-treated group: On the 3rd day after infection, the first focus of *Candida* infection was found in the retina, the choroidal membrane was thickened with infiltrates of both polymorphonuclear leukocytes (PMNs) and mononuclear cells (MNCs), and the capillaries in the periphery of the lesion were slightly dilated. In the lesion, the outer granular layer was disrupted and the margin was bent toward the choroidal membrane. The inflammatory infiltrate extended within the inner granular layer, but the inner limiting membrane was not altered (Fig. 4A). In the lesion, most of the observed fungal elements corresponded to yeast forms (Fig. 4B). On the 5th day, the choroidal membrane was also thickened due to the large numbers of infiltraing PMNs and MNCs. The inflammatory infiltrate extended to the whole layer of the retina and the inner limiting membrane was ruptured (Fig. 5A). Fungi were present in the area, showing PMNs infiltration, but no inflammatory cells were seen in the lower layer of the retina (Fig. 5B). On the 7th day, the choroidal membrane became thicker due to infiltration of MNCs, and the infiltration of PMNs became less marked. In a larger number of foci, the inner limiting membrane was ruptured and the whole layer of the retina was disrupted (Fig. 6A). There were few fungi showing a yeast form or short pseudohyphae on the vitreous surface of the lesion (Fig. 6B). On the 10th day, MNC infiltration was more marked than PMN infiltration in the whole lesion. There were no yeast cells in the lesion (Fig. 7). The sequential changes observed in this experimental group are summarized in Table 4.

1-2. Steroid-treated group: On the 3rd day, the first focus of *Candida* infection was also noted in the retina and involved the outer granular, outer plexiform, and inner granular layers (Fig. 8A). In the lesion, there was little MNCs infiltration without PMNs and *Candida* showed pseudohyphal and/or hyphal growth (Fig. 8B). In addition, one eyeball had yeast cells in the lumen of capillaries in the ciliary body (Fig. 9). On the 5th day, the choroidal membrane was slightly thickened because of PMN infiltration, the inner limiting membrane above it was ruptured, and clusters of PMNs including many fungi with hyphal growth were seen in the vitreous body (Fig. 10). On the 7th day, the lesion exhibited a dense, extensive PMN infiltration in which many fungi with hyphal

Table 1. Sequential change of number of lesions confimed by ophthalmoscopic examination

Group \ Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Non-treated	−	−	+	+	++	++	++	++	+	+	−	−	−	−
Steroid-treated		−	−	+	++	+++	+++	+++	+++	++	++			

Number of lesions: –, zero; +, 3 to 5; ++, 6 to 12; +++, more over.

Table 2. Summary of ophthalmoscopic findings

Finding of lesions \ Group	Non-treated	Steroid-treated
Position	Equator	Whole
Number	3 - 4	4 - 7
Color		
Lesions	Light white	Gravish white
Retina	Red	Pale
Color	Gravish white	Gravish gray
Border	Clear	Clear
Surface	Dry	Wet
Shape	Round	Round

Table 3. Difference of morphometric analysis

Characteristic of lesions	5th day		7th day	
	Non-treated	Steroid-treated	Non-treated	Steroid-treated
Number[1)]	4.67 ± 2.58	8.33 ± 3.20	10.5 ± 3.02	25.17 ± 5.91
Size (mm^2)[2)]	0.49 ± 0.27	0.99 ± 0.52	0.47 ± 0.26	0.91 ± 0.53
Distance (mm)[3)]	9.39 ± 2.83	8.96 ± 4.21	8.64 ± 3.99	9.28 ± 4.70

[1)]: Number of lesion observed by stereomicroscopy.
[2)]: Area of lesions.
[3)]: Distance of each lesions from the optic disc.

Table 4. Summary of histological findings of the lesions in non-treated group

Finding \ Day	1	3	5	7	10
Yeast	−	+	+	+	+
Psuedohypha	−	−	−	+	−
Hypha	−	−	−	−	−
PMNs	−	++	++	+	+
MNCs	−	+	+	++	+++

PMNs, polymorphonuclear leukocytes; MNCs, mononuclear cells.

Table 5. Summary of histological findings of the lesions in steroid-treated group

Finding \ Day	1	3	5	7	10
Yeast	−	+	+	+	+
Psuedohypha	−	+	+	++	+
Hypha	−	++	++	++	+
PMNs	−	+	+++	+++	+++
MNCs	−	+	+	+	+

Abbreviations are in Table 4.

or pseudohyphal growth were visible. Thickening of the choroidal membrane was not prominent and showed a much lesser MNC response compared to that of the non-treated group (Fig. 11). On the 10th day, the lesions were even larger but with no other histopathological changes (Fig. 12). The sequential changes are summarized in Table 5.

2. Histological findings of other organs: 2-1. Number of days elapsed before the lesion developed in different organs: Lesions developed in the kidneys on the 1st day after inoculation, in both experimental groups. In the brain and heart, foci were confirmed only in the steroid-treated group (Table 6).

2-2. Outline of findings in other organs: On the 1st day, *Candida* was found in the kidneys in both groups. However, the characteristics of *Candida* differed. While a few yeasts were found within capillaries of the glomeruli as microthrombi without PMN infiltration in the non-treated group, lesions in the steroid-treated group were characterized by elongation

Table 6. The day is the initially involvement of *Candida* in histopathologically

Organ	Non-treated	Steroid-treated
Eyes	3	3
Kidney	1	1
Brain	none	7
Heart	none	7
Liver	none	none

of hyphae, not only in capillaries but also in adjacent tubuli without any types of inflammatory infiltration. On the 3rd day or later, PMN infiltration was observed in the foci in both groups. The foci gradually increased in size and number, but more marked growth of *Candida* was observed in the steroid-treated groups during the study period. On the 10th day, foci in the non-treated group showed infiltration of MNCs and limited growth of yeast cells, while in the steroid-treated group there was extensive *Candida* growth with hyphae and pseudohyphae (Fig. 13). On the 7th day after infection, hyphae and/or pseudohyphae of *Candida* with much lesser infiltration of PMNs were detected in the brain and myocardium of rabbits treated with the steroid.

DISCUSSION

The first case of EFE was described by Miale in 1943 and was due to septicemia (17). In 1961, Hoffmann et al. established an experimental rabbit model of EFE by intravenous administration of *C. albicans*. They documented that the experimental EFE was started with the settlement of yeast cells in the choroid membrane followed by PMN infiltration (12-16).

C. albicans is recognized as the most frequent cause of EFE, and has been isolated in 85 to 99% of all reported cases (4-7). Candidemia is known as the most significant pathophysiological base of EFE, and usually occurs in patients treated with multiple antibiotics, patients undergoing abdominal surgery, patients receiving steroids administration, patients with long-standing intravenous catheters, patients administered immunosuppressives, and patients with diseases known to be associated with an impairment of the host defense mechanisms (8-11). However, there have been no experiments on immunocompromised animals with EFE (17-20).

We discuss herewith the pathophysiology of EFE based on the results of our comparative experimental study (immunocompetent versus immunocompromised) of sequential histological and ophthalmoscopic examinations.

We monitored the course of events by ophthalmoscopy from the first day after infection, and the first lesion was detected in the fundus on the 3rd day in both immunocompromised and immunocompetent rabbits. Histopathologically, the first changes were also found on the 3rd day in both groups. This fact suggests that ophthalmoscopy may be as useful for the diagnosis of EFE as histological examination.

Few authors have discussed the relationship between findings obtained by ophthalmoscopy and those obtained by histopathological examination in terms of the time of onset of ocular lesions in animal models of endogenous infection. In the present study, both ophthalmoscopic examination and morphometric analysis of retinal lesions in fixed eyeballs demonstrated that lesions appear on the equator of the eyeball and then spread toward the posterior pole. Most of the initial

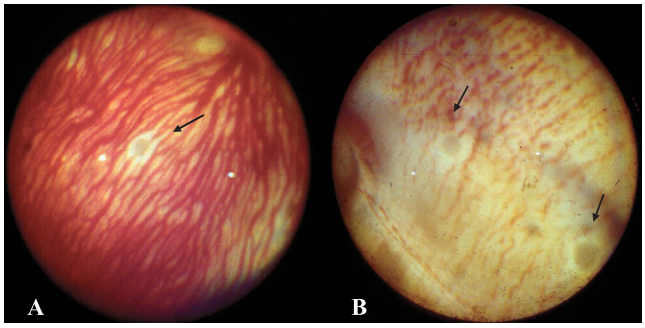

Fig.1. Lesions on the 3rd day with ophthalmoscopy. (A) Initial lesion of the non-treated group; (B) initial lesions of the steroid-treated group.

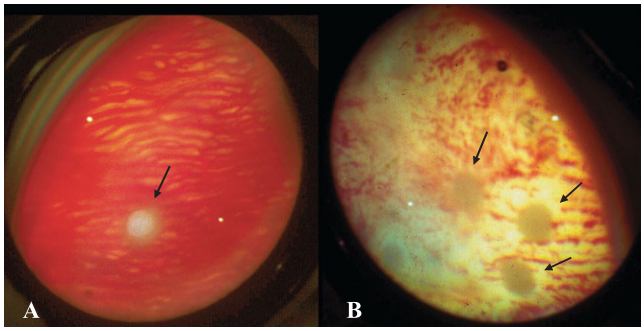

Fig. 2. Lesions on the 7th day with ophthalmoscopy. (A) Lesion of the non-treated group; (B) lesions of the steroid-treated group.

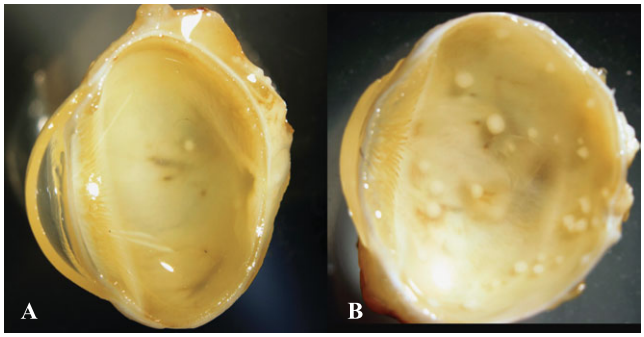

Fig. 3. Stereomicroscopic findings on the 7th day. (A) The non-treated group; (B) the steroid-treated group.

lesions consisted mainly of PMN infiltration of the choroidal membrane. EFE is established by fungal adhesion to the choroidal capillaries, followed by their growth and infiltration by PMNs. On the other hand, the choroidal membrane is supplied by two important vascular systems that branch out from the ophthalmic artery. One is the group of short pos-terior ciliary arteries that consist of 12 to 15 branches from the ophthalmic artery; these arteries enter the choroidal membrane around the optic nerve, then distribute into the choroid from the equator backward. The other is a group of long posterior ciliary arteries formed by two vessels which distribute into the choroid from the equator forward (21). In addition, the equator of the eyeball, where the first *Candida* lesion was found to have developed in our study, is characterized by capillaries that communicate with the arterioles from the anterior and posterior parts of the eyeball to form the choroidal network. This is drained by the vortex veins, which are the most important efferent channels of the eyeball (21-23) (Fig. 14). Accordingly, the part is speculated that there is abrupt decreasing of shear stress in rheologically,

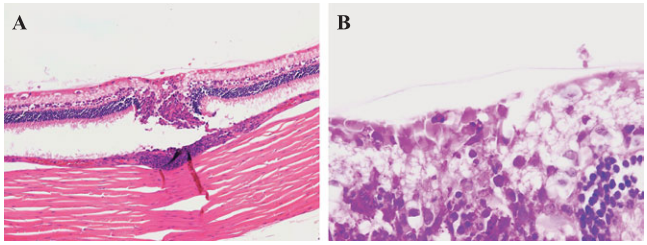

Fig. 4. Lesion on the 3rd day in the non-treated group (A, H&E stain × 200; B, PAS stain × 1,000).

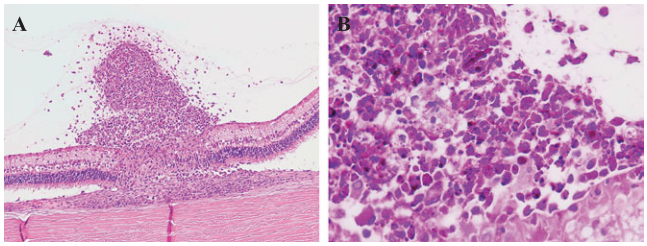

Fig. 5. Lesion on the 5th day in the non-treated group (A, H&E stain × 200; B, PAS stain × 1,000).

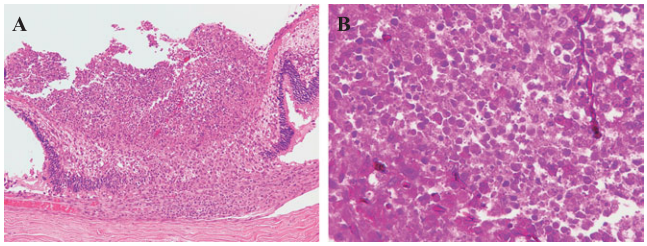

Fig. 6. Lesion on the 7th day in the non-treated group (A, H&E stain × 200; B, PAS stain × 1,000).

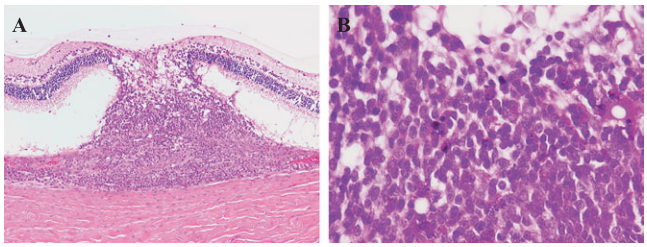

Fig. 7. Lesion on the 10th day in the non-treated group (A, H&E stain × 200; B, PAS stain × 1,000).

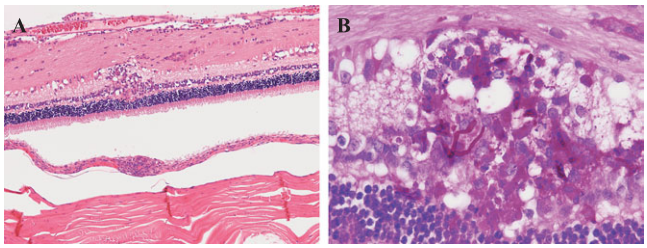

Fig. 8. Lesion on the 3rd day in the steroid-treated group (A, H&E stain × 200; B, PAS stain × 1,000).

therefore adhesion of yeast cells onto the endothelial cells is presumed easily. After the initial lesions appear in the equator, they spread toward the posterior pole that is supplied by the short posterior ciliary arteries. In addition, the choriocapillaries of the posterior pole comprise the most complex plexus, and

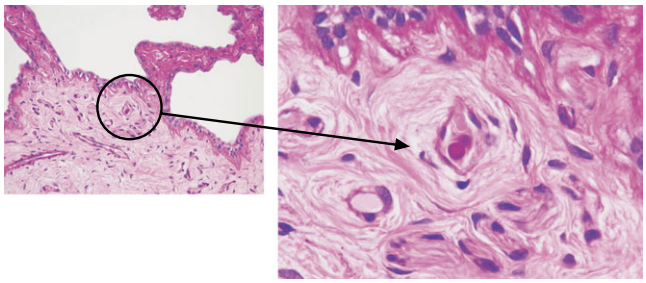

Fig. 9. Adherent yeasts in ciliary body on the 3rd day in the steroid-treated group (PAS stain × 400).

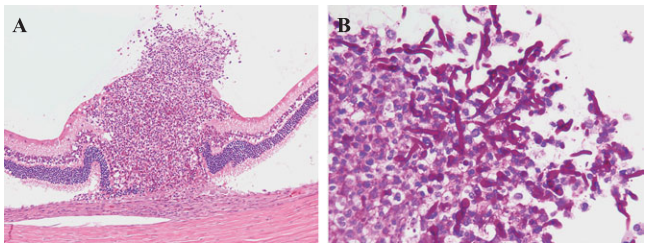

Fig. 10. Lesion on the 5th day in the steroid-treated group (A, H&E stain × 200; B, PAS stain × 1,000).

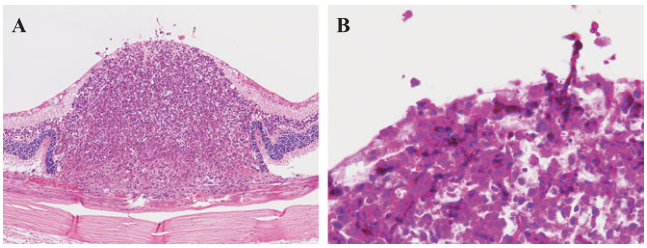

Fig. 11. Lesion on the 7th day in the steroid-treated group (A, H&E stain × 200; B, PAS stain × 1,000).

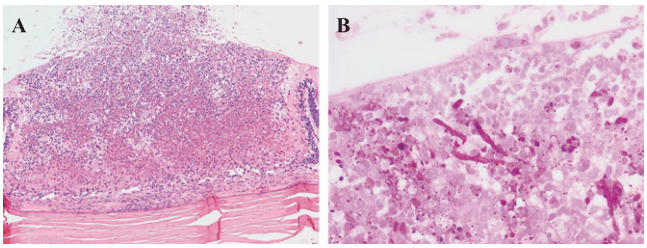

Fig. 12. Lesion on the 10th day in the steroid-treated group (A, H&E stain × 200; B, PAS stain × 1,000).

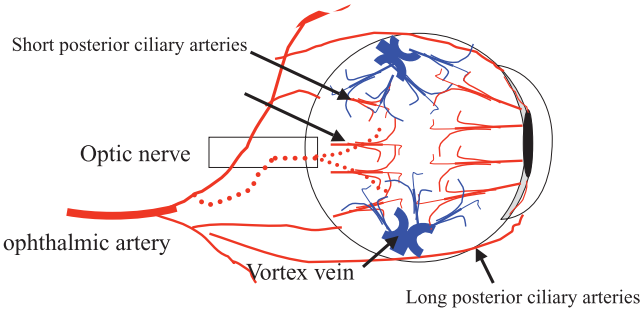

Fig. 14. Scheme of uveal blood vessels (red line is artery, blue one is vein). Many arteries from long posterior ciliary arteries and short posterior ciliary arteries anastomose and effluxto vortex vein at the equator of the eye.

has a fenestrated endothelium; these factors may contribute to the adhesion of yeasts to endothelial cells (21-23).

On the other hand, Edwards et al. documented the presence of fungi in the choroidal capillaries 15 min after the inoculation of *C. albicans* (13). Hoffman detected fungi in the ciliary body a few hours after the inoculation of *C. albicans* (12). In our experiment, we also observed that yeast adhered to the ciliary body on the 3rd day. The yeast was assumed to have reached the choroidal capillaries via the long posterior ciliary arteries. Accordingly, fungal invasion of the posterior pole was assumed that to adhere the choroidal capillary mainly via the short posterior ciliary arteries. We speculated that the number of lesions depended on the number of fungi, that is, on the inflow rate of blood. However, despite the extensive and marked PMN infiltration of the choroid in an individual animal, we found no cellular infiltration in the ciliary body.

Hirano found vitreous opacity in an animal model of EFE by ophthalmoscopy, on the 8th to 12th day after the infection with of *C. albicans* (16). In our experiment, none of the rabbits showed vitreous opacity during the observation period by ophthalmoscopy, but a dense cluster of PMNs including yeast cells with a ruptured inner limiting membrane was observed histopathologically. Thus, as yeasts are suspected to enter the vitreous body from the choroid, when a lesion is detected by ophthalmoscopy and there is no vitreous opacity, it is important to emphasize the possibility of EFE rapidly progressing to diffuse endophthalmitis with the immediate involvement of the entire vitreous body.

Although it is well known that an immunocompromised condition is a risk factor for the development of EFE, only a few studies have been performed using a model of immuno-

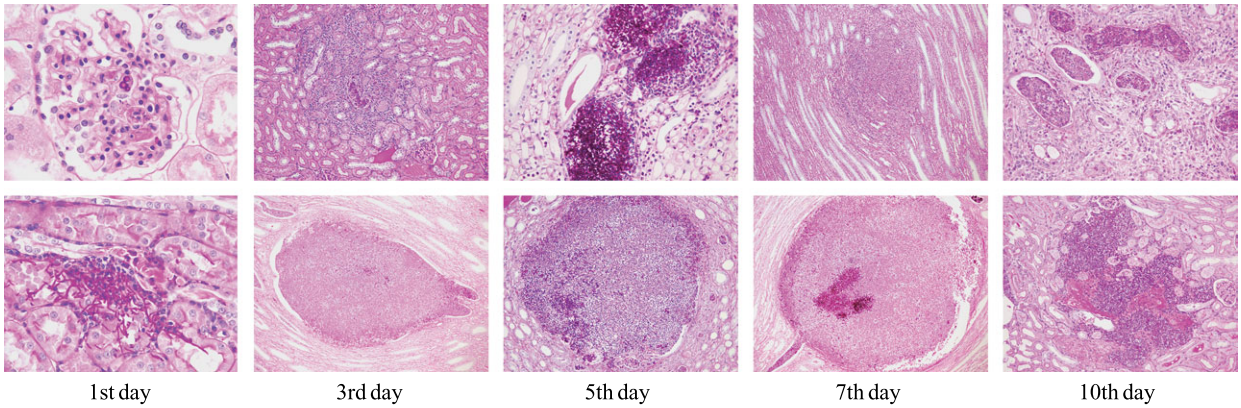

Fig. 13. Histological changings of kidney. Upper is the non-treated group's and lower is the steroid-treated group's (PAS stain).

compromised EFE induced by inoculating of other hyphae. Aziz and Mayoyo reported a model of immunocompromised EFE induced using filamentous fungi such as *Aspergillus fumigatus*, *Pseudallescheria boydii*, and *Fusarium solani*, but no detailed analyses were given (18-20). In addition, no experimental study using *Candida* in a model of immunocompromised EFE has been reported, although endophthalmitis is known to be the most frequent disease in immunocompromised patients.

Our findings for the two rabbit models can be summarized as follows. The period and distribution of development were equivalent, but the number and the size lesions were larger in the steroid-treated group. Histopathologically, the degree of PMN infiltration was equivalent in the two experimental groups, but the appearance of PMNs was delayed in the steroid-treated group, and the number of fungi was higher in this group, with most of them being in the hyphae and/or pseudohyphae state.

Steroids are widely used in clinical practice in situations requiring modulation of the inflammatory response. However, it is well documented that the function of PMNs is impaired by steroid treatment (24-31). PMNs are important components of the initial inflammatory response. On the other hand, the precise mode of action of steroids is uncertain, although it has been reported that steroids reduce PMNs adhesion (24-29), intracellular bacterial killing activity (29), and egress of inflammatory cells from the vessels into tissues (30-32). In addition, recent studies have shown that at high doses steroids reduce the chemotactic response, superoxide production, and degranulation of PMNs (33).

Candida was presumed to have rapidly proliferated to pseudohyphae and/or hyphae after inoculation. Then, PMN infiltration occurred but fungal growth and invasion were not suppressed because of the low phagocytic activity and fungi killing activity of PMNs. Hirano reported that the most frequent fungal form in ocular lesions was yeast, with few pseudohyphae (16). Direction of the development was vertical, involving the retina to vitreous. We speculated that the cellular framework of the sclera and retina influenced the direction of progress of the disease. Gupta et al. reported that it is possible to induce EFE in healthy people by a bolus dose of fungi injected intravenously, based on the development of EFE in 13 immunocompetent people who received contaminated intravenous fluid (34). Our results also suggested that EFE could develop in immunocompetent subjects, because a bolus dose of fungi induced EFE in immunocompetent rabbits. However, EFE is presumed to resolve with no symptoms in immunocompetent subjects.

Systemic candidiasis tends to cause lesions in the lungs, kidneys, heart, liver, spleen, and brain. Furthermore, fungemia develops 6 to 58 days after catheterization and visual symptoms appear 3 to 15 days after blood cultures of the patients turn positive (35,36). Many researchers noted that *Candida* was observed in the kidneys, brain, liver, and spleen, but not in the eyeballs (13-16,37-39). However, only a few reported the time of onset of the initial event or a comparative histopathological examination of the ocular lesion and those in other organs.

Edwards et al. observed that EFE appeared on the 5th day (13), and Hirano between the 5th and 10th day (16). In our experiment, EFE was observed on the 3rd day after inoculation of *Candida*. Fungi were found in the kidneys on the 1st day in both groups. That is, there was no difference between the two groups. And the lesions in the kidneys correlated with the ocular lesions with respect to PMN infiltration, the number and form of fungi, and the sequence of histopathological changes. In addition, fungi were observed in the brain and cardiac muscle.

A common characteristic of renal glomeruli and the choroid is the presence of numerous capillaries and endothelial fenestration (23). The initial change in the renal lesion is too small to detect at an early stage. It is difficult to detect a renal lesion by echography in the early phase or the initial change by blood or urine biochemistry. It is not easy that to get the lesion correctly, if the biopsy is carried out, it dose not necessary catch the lesion.

In previous studies, the frequency of EFE in patients with candidemia was found to vary between approximately 10 and 40% (1-4), although Scherer and Lee reported an occurrence of only 2.8%, and considered that the reason for this low incidence was the adequate antifungal therapy the patients had received before the ophthalmologic consultation (36). Therefore, it may be said that early diagnosis and adequate treatment of systemic fungal infection will substantially decrease the occurrence of EFE.

Based on our findings, we think that, once candidemia has occurred, a choroidal lesion may develop followed by renal lesions. Consequently, we emphasize the importance of ophthalmoscopic examination to detect EFE at an early stage. Moreover, this examination may be useful to monitor the degree of the progress of candidemia, development of lesions and systemic involvement in patients with candidemia.

ACKNOWLEDGMENTS

This study was supported by Teikyo University Institute of Medical Mycology and the Health and Labour Sciences Research Grants on the research on measures for intractable diseases from the Ministry of Health, Labour and Welfare, Japan (grant17243601).

We thank Dr Masakazu Matsuhashi, Professor of 1st Department of Ophthalmology at Toho University School of Medicine, for his thoughtful review and suggestions.

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