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Prediction based on Routine Serological Test Values of Fungal Infection Patients whose Condition may become Serious

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A method was developed for predicting which patients with suspected fungal infection may have their condition become serious based on routine serological test values. Of the 87 hospitalized patients who were subjects in this study, 43 had their condition become serious and died during hospitalization (mortality of 49.4%). The 87 cases were classified into 2 groups based on WBC (white blood cell) counts. The number of cases with WBC counts over 10,000 was 68 (an incidence of 78.2%), and 35 of 68 subjects in the group died during hospitalization (mortality of 51.4%). The number of cases with WBC counts never exceeded 10,000 was 19 (an incidence of 21.8%), and 8 of 19 subjects in the group died during hospitalization (mortality of 42.1%). WBC tend to increase in patients with infection, but there is no causal relation ship between WBC counts and mortality. Moreover, the 87 cases were classified into 2 groups based on AST, ALT and BUN value. The group with patients whose AST (or ALT) values exceeded 100 IU/mL or BUN value exceeded 100 mg/dL was 43 (an incidence of 49.4%), and 26 of 43 subjects in the group died during hospitalization (mortality of 60.5%). The group with patients whose AST (or ALT) values did not exceed 100 IU/mL or BUN value did not exceed 100 mg/dL was 44 (an incidence of 50.6%), and 17 of 44 subjects in the group died during hospitalization (mortality of 38.6%). As the mortality of the group whose AST, ALT and BUN values showed abnormal was higher than the mean mortality of the 87 hospitalized patients, these values becomes a index to predict patients whose condition may become serious. Moreover, the 87 cases were classified into 4 groups based on WBC counts and AST, ALT and BUN values, in order to select patients whose condition may become serious. The group with patients whose WBC count of over 10,000 (cells/mL) when either AST (or ALT) exceeded 100 IU/mL or BUN exceeded 100 mg/dL was 36 (an incidence of 41.3%), and 24 of 36 subjects in the group died during hospitalization (mortality of 66.7%). Sixteen of 24 death cases in the group died within 50 days after developing the risk condition.

These results indicated that serological test values such as WBC, AST, ALT and BUN can be used as an indicator to predict which patients may have their condition become serious.

Key Words: routine serological test value, fungal infection, AST, ALT, BUN

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Introduction

With the development of a medical technology and the medical therapy, the treatment results of various kinds of diseases improve clearly in late years, and the average life span of the Japanese citizen shows a tendency toward the increase in these years. However, pneumonia is located in the fourth place of the cause of death in the vital statistics, and the incidences of a pneumonia increase at person of advanced age[1].

There are many person of advanced age who has an underlying diseases or decline in immunity, and these conditions are considered to be a factor why the infectious disease turns worse.[2,3,4] The medical treatments such as long-term hospitalization, indwelling catheter in the blood vessel or urethra catheter raise a risk of the opportunistic infection. Especially the incidence of fungal infection is increased in these risk states.[5,6,7]

If an infectious disease patient has few risk factors, most of the patient is cured by use of appropriate antimicrobial. However, when the patient who has many risk factors is infected with rebelliousness infectious diseases such as deep mycosis, the condition tend to become serious.[8,9,10] Even if the patient of rebelliousness infectious diseases, a mortality may reduce by prediction of patient whose condition become serious and an appropriate treatment. To develop the method of predicting patient whose condition develop into serious, the result of serological test values was retrospectively analyzed. We described here that serological test values such as WBC, AST, ALT and BUN can be used as an indicator to predict which patients may have their condition become serious.

Object and Method

Objects

Analysis was conducted on hospitalized patients with fungal infections at hospital in Yamagata prefecture during from January, 2008 to December, 2009. The number of patients was 87 (mean age±SD: 77.6±12.9), male was 50 (mean age±SD:73.7±14.6), and female was 37(mean age±SD:82.7±7.7). In this study, the patients with positive result of fungal test were selected as patients with fungal infections. The positive conditions of the fungal test are(1) detection of fungal cells by culture inspection, (2) the cutoff value of candida antigen by latex agglutination test is more than double, (3) the amount of Aspergillus antigen in serum is more than 1.5 ng/mL, and (4) the amount of β-D-glucan is more than 11 pg/mL. [11,12,13]

Candida albicans was detected from most of these patients. *C. glabrata*, *C. tropicalis* and *C. parapsilosis* were detected several patients. These fungal cells were found in an expectoration, mail, urine, and a tip of the catheter. These patients were treated by antifungal agents. The dosage period and dose of antifungal agents were described in Table 1.

The background of 87 case is that an internal disease

Table 1. Dosage period and dose of antifungal agents

	Case : 43 (Antifungal agents,Dose)		Dosage period (mean day± SD)
Death group	MCFG 50mg/day	12 case	8.5± 6.4day
	MCFG 100mg/day	17 case	9.4± 8.1day
	MCFG 150mg/day	4 case	6.7± 3.8day
	MCFG 170mg/day	1 case	21day
	F-FLCZ 200mg/day	8 case	17.0± 16.6day
	F-FLCZ 400mg/day	1 case	20day

	Case : 44 (Antifungal agents,Dose)		Dosage period (mean day± SD)
Discharge group	MCFG 50mg/day	9 case	6.8± 1.8day
	MCFG 77mg/day	2 case	22day
	MCFG 77.5mg/day	1 case	40day
	MCFG 86mg/day	1 case	25day
	MCFG 100mg/day	15 case	11.1± 3.8day
	MCFG 150mg/day	1 case	10day
	MCFG 200mg/day	2 case	8day
	F-FLCZ 100mg/day	2 case	5.5day
	F-FLCZ 200mg/day	6 case	11.0± 6.3day
	F-FLCZ 400mg/day	4 case	9.7± 2.3day
	VRCZ 400mg/day	1 case	13day

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MCFG : Micafungin Sodium

F-FLCZ : Fosfluconazole

VRCZ : Voriconazole

is 45 and an surgical disease is 42. A disease at the time of the hospitalization are 5 cases of cardiovascular system, 18 cases of respiratory system, 37 cases of digestive system, 15 cases of Cerebral blood vessel system, 3 cases of Kidney/urinary system, 3 cases of Blood/blood-forming organ system, 2 cases of Mind/nervous system and 4 cases of others. Of the 43 patients who died during hospitalization, 7 patients were died by fungal infection. In addition, a heart trouble, a lung disease, blood dyscrasia, cancer, and a cerebropathy were diagnosed as the cause of death.

The serological test values and prognoses of these patients were examined.

Classification based on values of serological testing

The dangerous levels of the serological testing are described below. WBC counts which exceeded 10,000 cells/ μ L are an index of infectious disease.[14,15,16] Haneda et al reported that the mortality rate is increased when AST values exceeded 60 IU/mL or ALT values exceeded 80 IU/mL.[17] In this study, we considered the value of more than 100 IU/mL as attention value. As 100 mg/dL of BUN is an index of renal insufficiency (Uremia), [14] we considered that more than 100 mg/dL is to be dangerous levels. Eighty seven subjects were classified based on WBC (white blood cells) counts, AST (aspartate aminotransferase), ALT (alanine aminotransferase) and BUN (blood urea nitrogen) values. The units for the test items listed in this paper are cells/ μ L for WBC, IU/mL for AST, IU/mL for ALT, and mg/dL for BUN.

(1) A group with patients whose WBC counts never exceeded 10,000 and whose AST, ALT and BUN values never exceeded 100 during hospitalization.
(2) A group with patients whose WBC counts did not exceed 10,000 when AST, ALT and BUN values exceeded 100 during hospitalization.
(3) A group with patients whose ALT, AST, and BUN values did not exceed 100 when WBC counts exceeded 10,000 during hospitalization.
(4) A group with patients whose WBC counts exceeded 10,000 when AST, ALT, and BUN values exceeded 100 during hospitalization.

Results

Relationship of WBC and mortality

We examined whether the number of WBC became the index to predict the condition of patient. Eighty seven cases that were study subjects were classified into 2 groups based on WBC counts. As shown in Table 2, the number of cases with WBC counts over 10,000 was 68 (an incidence of 78.2%), and 35 of 68 subjects in the group died during hospitalization (mortality rate of 51.4%). The number of cases with WBC counts never exceeded 10,000 was 19 (an incidence of 21.8%), and 8 of 19 subjects in the group died during hospitalization (mortality rate of 42.1%). It is well known that the number of cases with WBC counts over 10,000 was increased in the patients of infectious disease. This result agreed with a report of that WBC counts which exceeded 10,000 are an index of infectious disease.[16] Since the mortality of the cases with WBC counts over 10,000 was higher than that of the cases with WBC counts never exceeded 10,000, it was suggested that the increase of WBC mean that the inflammation state turned worse. However, the mortality rate of the cases with WBC counts over 10,000 (51.4%) was similar to that of total case (49.4%). Thus, we considered that only with WBC count, the prediction of patient whose condition may become serious is difficult.

The relationship between AST, ALT and BUN values and mortality

When fungal cells such as *Candida albicans* infected in animals, the cells were located at liver and kidney.[18] The pathogen may injure a liver and a kidney function and lead to serious condition. Thus, we consider the relationship between AST, ALT and BUN values and mortality. The values of AST and ALT exhibit more than 100 when the patient is in impaired liver function.[17] The values of BUN exhibit more than 100 when the patient is in impaired renal function.[14] Thus, we examined the mortality of the infectious diseases patient, when the values of AST, ALT or BUN were more than 100. As shown in Table 2, the group with patients whose AST (or ALT) values exceeded 100 IU/mL or BUN value exceeded 100 mg/dL was 43 (an incidence of 49.4%), and 26 of 43 subjects in the group died during hospitalization (mortality rate of 60.5%). The group with patients whose AST (or ALT) values did not exceed 100 IU/mL or BUN value did not exceed 100 mg/dL was 44 (an incidence of 50.6%), and 17 of 44 subjects in the group died during hospitalization (mortality rate of 38.6%). As the mortality of the group whose AST, ALT and BUN values showed abnormal was

higher than the mean mortality of the 87 hospitalized patients, we considered that these values becomes a index to predict patients whose condition may become serious.

Classification based on values of serological testing and mortality

The number of WBC is used for prediction of inflammation state, and the values of AST, ALT and BUN are useful for prediction of the patient who impaired liver and kidney. Therefore, we expected that when these risk factors are appeared at same time, the fatal damage occurs. To confirm this anticipation, 87 cases that were study subjects were classified into 4 groups based on WBC counts, AST, ALT, and BUN values in order to calculate the mortality rate of each group. It was found that for the group that met the condition of a WBC count of over 10,000 (cells/mL) when either AST (or ALT) exceeded 100 IU/mL or BUN exceeded 100 mg/dL, the mortality rate was high, at 66.7% (Table 3). Thus, we called this group a risk condition.

The number of died cases in the group of the risk condition was 24. Sixteen of 24 cases were died within 50 days since the outbreak of risk condition (Table 4). The frequency of risk condition was calculated based on the survival time and number of outbreak of risk condition described in Table 4. The outbreak frequency of the risk condition of these patients was once in 19.8±23.0. Because serum examination is usually performed every 3-7 days, it was clarified that the outbreak of risk condition is transient. Thus, we expected that the rate of detection of the risk condition can be enhanced by increasing examination of WBC, AST, ALT and BUN.

Table 2. The relationship between WBC, AST, ALT, BUN values and mortality

	Number of Died cases/total	Mortality(%)
Total cases	43 / 87	49.4
Cases whose WBC counts never exceeded 10,000	8 / 19	42.1
Cases whose WBC counts exceeded 10,000	35 / 68	51.4
AST, ALT, or BUN values never exceeded 100	17 / 44	38.6
AST, ALT, or BUN values exceeded 100	26 / 43	60.5

Table 3. Classification based on values of serological testing and mortality

	Number of Died cases/total	Mortality(%)
Total cases	43/87	49.4
Cases whose WBC counts never exceeded 10,000 and AST, ALT, and BUN values never exceeded 100	6/12	50.0
Cases whose WBC counts did not exceed 10,000 when AST, ALT, and BUN values exceeded 100	2/7	28.6
Cases whose AST, ALT, and BUN values did not exceed 100 when WBC counts exceeded 10,000	11/32	34.3
Cases whose WBC counts exceeded 10,000 when AST, ALT, and BUN values exceeded 100	24/36	66.7

Table 4. Survival time of patient with risk condition

No. of patient	Survival time ※1 (days)	Number of outbreak ※2 of risk condition	No. of patient	Survival time ※1 (days)	Number of outbreak ※2 of risk condition
1	150	4	13	63	5
2	0	1	14	4	1
3	2	2	15	36	6
4	123	2	16	38	3
5	1	1	17	70	2
6	68	3	18	26	3
7	10	2	19	33	3
8	36	3	20	41	1
9	96	14	21	21	3
10	97	1	22	29	2
11	9	2	23	8	1
12	43	2	24	90	2

※1 Survival time from the outbreak of risk condition
※2 Number of outbreak of risk condition during hospitalization

Table 5. The relationship of the medical treatment and the outbreak of risk condition

	Catheter insertion	Operation
Total cases	78 / 87 (89.7%)	16/87 (18.4%)
Cases whose WBC counts never exceeded 10,000 and AST, ALT, and BUN values never exceeded 100	11 / 12 (91.7%)	1/ 12 (8.3%)
Cases whose WBC counts did not exceed 10,000 when AST, ALT, and BUN values exceeded 100	6 / 7 (85.7%)	2/ 7 (28.6%)
Cases whose AST, ALT, and BUN values did not exceed 100 when WBC counts exceeded 10,000	26 / 32 (81.3%)	4 /32 (12.5%)
Cases whose WBC counts exceeded 10,000 when AST, ALT, and BUN values exceeded 100	35 / 36 (97.2%)	9/36 (25.0%)

The relationship of the medical treatment and the outbreak of risk condition

Since the insertion of a catheter and an operation become the risk factor of the infectious disease, we examined whether a surgical management causes the outbreak of risk condition. As shown in Table 5, the incidence of risk condition of the patients who was inserted a catheter or operated was not increased, so we considered that these surgical treatment was not a direct cause of the risk condition.

Discussion

Early detection and early treatment are considered to be an ideal and basics of treatment. However, there are few diagnosis method to predict patients whose condition may become serious. Actually, most of pathological changes are diagnosed by a clinical symptom. The surgical treatments and underlying disease caused immune-compromised condition. A systematic fungal infection tend to occur in this conditions and induce serious condition. [19,20] The

mortality of candidiasis (10 to 19%) is not changed in these years in spite of that newly antimicrobial for Candida infection has developed.[20,21] A delay of the treatment start, an insufficient period for treatment and a risk factors such as a tumor, an indwelling catheter in the blood vessel and steroid medicine may be a reasons why curative effect is not improved.[18] In this study, we described here that serological test values can be used as an indicator to predict which patients may have their condition become serious.

Eighty seven cases with fungal infectious disease were classified into 4 groups based on WBC, AST, ALT and BUN values, in order to calculate the mortality rate for each group. It was found that for the group that met the condition of a WBC count of over 10,000 when either AST, ALT or BUN exceeded 100, the mortality rate was higher than that of other group (Table 3). Since this risk condition can become the index to predict whether the patient become worse, we analyzed the relationship between the incidence and the survival time of risk condition. In 24 death cases in a risk condition, 18 of the patients died after more than 10 days from outbreak of risk condition (Table 4). Moreover, the occurrence of the risk condition was not continuous. These results indicated that the risk condition is not a direct cause of death. Thus, we expected that a secondary obstacle which was based on an impairment of liver and kidney induced a fatal factor.

We described here that the results of routine serologic test can be applied for prediction of metabasis of mycoses patients. As a future problem, we must clarify the mechanism of the outbreak of risk condition.

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