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Epidemiology of Visceral Mycoses: Analysis of Data in *Annual of the Pathological Autopsy Cases in Japan*

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The data on visceral mycoses that had been reported in the *Annual of the Pathological Autopsy Cases in Japan* from 1969 to 1994 by the Japanese Society of Pathology were analyzed epidemiologically. The frequency of visceral mycoses among the annual total number of pathological autopsy cases increased noticeably from 1.60% in 1969 to a peak of 4.66% in 1990. Among them, the incidences of candidiasis and aspergillosis increased the most. After 1990, however, the frequency of visceral mycoses decreased gradually. Until 1989, the predominant causative agent was *Candida*, followed in order by *Aspergillus* and *Cryptococcus*. Although the rate of candidiasis decreased by degrees from 1990, the rate of aspergillosis increased up to and then surpassed that of candidiasis in 1991. Leukemia was the major disease underlying the visceral mycoses, followed by solid cancers and other blood and hematopoietic system diseases. Severe mycotic infection has increased over the reported 25-year period, from 6.6% of the total visceral mycosis cases in 1969 to 71% in 1994. The reasons for this decrease of candidiasis combined with an increase of aspergillosis or of severe mycotic infection might be that (i) nonsevere (not disseminated) infections were excluded from the case totals, since they have become controllable by antifungal drugs such as fluconazole, but (ii) the available antifungal drugs were not efficacious against severe infections such as pulmonary aspergillosis, and (iii) the number of patients living longer in an immunocompromised state had increased because of developments in chemotherapy and progress in medical care.

Recently many reports have described an increase of systemic fungal infections, which included aspergillosis (7, 14), zygomycosis (10), fusariosis (48), and candidiasis due to non-*Candida albicans Candida* spp. (9). Cutaneous or superficial candidiasis has seemed to be controllable by using effective azoles; however, azole-resistant *C. albicans* strains and pathogenic non-*C. albicans Candida* species have been emerging (5, 9, 49). Furthermore, severe systemic aspergillosis has been increasing in bone marrow-transplanted patients (4) and in those with other immunocompromised conditions (3).

Over the past 30 years, medical mycologists and pathologists have published several papers on the trends of mycoses (15, 16, 38, 45–47). Groll et al. (14, 15) reported the trends of invasive fungal infections from autopsy findings at the university hospital of Frankfurt, Germany, and Kappe et al. (39) presented analyzed data for invasive aspergillosis cases culled from autopsy records in Heidelberg, Germany. In Japan, several studies analyzing data on mycoses from autopsies had been reported previously; however, few reports on recent trends existed. A study by Miyake and Okudaira covered the 13 years between 1948 and 1961 (45), and a study by Hotchi et al. covered the 10 years between 1966 and 1975 (16). Okudaira et al. then reported the analyzed data from 1972 to 1981 (47), and now this report covers the period after that. As we also wanted to know the impact of new antifungal drugs such as fluconazole or itraconazole, we concentrated our study on the period after 1989. To discern trends in visceral mycoses, we have epidemiologically analyzed the data on visceral mycoses that had been reported in the *Annual of the Pathological Autopsy Cases in Japan* (18–37). As we reported previously, the total numbers of mycosis cases had been increasing until 1990, whereas the number of candidiasis cases had stopped increasing and had begun to decrease after 1989 (42, 43). Aspergillosis cases were not decreasing but maintained the highest rate of mycosis among the total autopsies. In this report, we review the recent trends and also analyze the effect of antifungal agents introduced in the clinical setting.

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MATERIALS AND METHODS

Diagnostic criteria. The criteria for the pathological diagnosis of each class of mycosis to be described in the *Annual of the Pathological Autopsy Cases in Japan* are not defined definitively by the Japanese Society of Pathology. Basically, the description of each case is the responsibility of the reporting pathologist and depends on his or her ability to make a diagnostic determination. Most of the autopsies included both gross and histopathological examinations; however, all of the pathologists could not be expected to be equally rigorous in their examination. There might be some differences among the pathologists deriving from their individual experiences with mycoses. Concerning fungemia or candidemia, reporting pathologists might have been given some clinical information on fungemia from the patient's medical records.

Definitions. Mycoses were defined as infections caused by eumycotic organisms such as *Candida*, *Aspergillus*, *Cryptococcus*, Zygomycetes, and other fungal species. Infections caused by filamentous bacteria such as Actinomycetes (*Actinomadura*, *Nocardia*, and *Streptomyces* spp.) and pneumonia caused by *Pneumocystis carinii* were excluded from the criteria for mycoses. Superficial infections such as dermatophytoses were excluded from the category of visceral mycoses. The term complicated infection means a mixed infection with more than two species of fungi. Cultures from specimens might be identified as containing more than two kinds of fungi.

The severe mycotic infections from autopsy records could be defined as (i) the direct cause of death; (ii) severe pulmonary infection involving both lobes of the lung; (iii) severe visceral infections of two or more organ systems, including those involving the central nervous system; (iv) multiorgan systemic infection of three or more organ systems; or (v) fungemia.

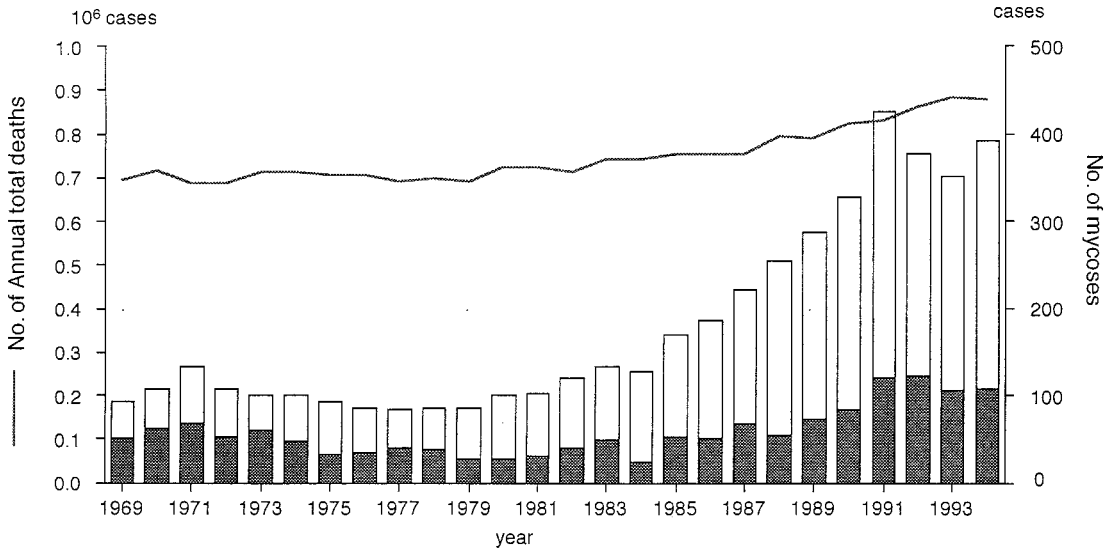

FIG. 1. Annual trends of total deaths and of deaths certified as resulting from mycoses in Japan. Data were extracted from *Vital Statistics of Japan*, edited by the Minister's Secretariat, Ministry of Health and Welfare (50) for the years 1969 through 1994. ——, number of annual total deaths; ▨, candidiasis cases; ▭, other mycosis cases.

Data collection. Data on visceral mycoses occurring in Japan from 1969 to 1994 were collected in the *Annual of the Pathological Autopsy Cases in Japan*, which was published from 1970 to 1995 by the Japanese Society of Pathology (18–37). Those data were extracted and compiled to make a database for analysis; however, data from the years 1982 to 1988, except 1985, were not used in this study.

Cases of stillborn babies were excluded from each annual total number of autopsy cases. The data for annual total deaths and the number of certified deaths from mycoses were from *Vital Statistics of Japan*, edited from 1969 to 1996 by the Minister's Secretariat, Ministry of Health and Welfare (50). The data were compiled into a database by using Filemaker Pro version 3.0, supplied by Claris Co., with a Power Macintosh 7100 (Apple Computer Co.).

RESULTS

In recent years, the annual total number of deaths in Japan has been about 900,000. Among these, about 3% of bodies are examined by pathological autopsy. Figure 1 shows that among the total deaths, the frequency of mycotic infection or candidiasis as the certified direct cause of death had increased noticeably from 1979 until 1991 (50).

The occurrence of mycoses among total autopsy cases from 1969 to 1994 in Japan is shown in Table 1. The frequency of

TABLE 1. Changes in rates of mycoses among total autopsy cases and of causative agents of mycoses from 1969 to 1994 in Japan

Yr	Total no. of autopsies	Total no. of mycoses	% of mycoses among total autopsies	% of cases among total mycoses (% of cases among total autopsies)						
				Candida	*Aspergillus*	*Cryptococcus*	Zygomycetes	Other	Unknown[a]	Complicated[b]
1969	24,715	396	1.60	25.8 (0.41)	24.5 (0.39)	8.8 (0.14)	0.8 (0.01)	0.3 (0.00)	37.6 (0.60)	2.3 (0.04)
1970	23,599	407	1.72	27.0 (0.47)	21.1 (0.36)	9.6 (0.17)	4.7 (0.08)	0.5 (0.01)	34.6 (0.60)	2.5 (0.04)
1971	23,245	433	1.86	28.9 (0.54)	24.7 (0.46)	9.9 (0.18)	3.7 (0.07)	0.2 (0.00)	28.9 (0.54)	3.7 (0.07)
1972	22,769	379	1.66	38.8 (0.65)	31.7 (0.53)	14.0 (0.23)	2.9 (0.05)	0.0 (0.00)	7.7 (0.13)	5.0 (0.08)
1973	23,274	466	2.00	37.8 (0.76)	23.4 (0.47)	12.7 (0.25)	1.3 (0.03)	0.0 (0.00)	21.7 (0.43)	3.2 (0.06)
1974	23,111	531	2.30	35.4 (0.81)	22.6 (0.52)	8.5 (0.19)	1.9 (0.04)	0.2 (0.00)	27.9 (0.64)	3.6 (0.08)
1975	23,048	620	2.69	34.5 (0.93)	17.3 (0.46)	8.1 (0.22)	2.9 (0.08)	0.0 (0.00)	34.5 (0.93)	2.7 (0.07)
1976	24,093	621	2.58	43.0 (1.11)	21.4 (0.55)	9.5 (0.24)	2.3 (0.06)	1.1 (0.03)	18.4 (0.47)	4.3 (0.11)
1977	25,897	664	2.56	37.5 (0.96)	22.6 (0.58)	6.9 (0.18)	3.5 (0.09)	0.2 (0.00)	25.3 (0.65)	4.1 (0.10)
1978	30,742	813	2.64	43.1 (1.14)	23.2 (0.61)	8.2 (0.22)	3.3 (0.09)	1.8 (0.05)	16.9 (0.45)	3.4 (0.09)
1979	32,844	861	2.62	35.4 (0.93)	21.7 (0.57)	9.1 (0.24)	3.0 (0.08)	0.0 (0.00)	25.9 (0.68)	4.9 (0.13)
1980	35,943	970	2.70	49.2 (1.33)	20.7 (0.56)	7.3 (0.20)	3.2 (0.09)	0.0 (0.00)	15.1 (0.41)	4.5 (0.12)
1981	38,841	1,096	2.82	42.0 (1.18)	26.0 (0.73)	7.4 (0.21)	3.8 (0.11)	0.1 (0.00)	15.0 (0.42)	5.7 (0.16)
1985	39,333	1,558	3.96	41.6 (1.65)	30.7 (1.22)	6.5 (0.26)	3.6 (0.14)	0.8 (0.03)	11.0 (0.44)	5.7 (0.23)
1989	37,557	1,672	4.45	42.3 (1.89)	30.1 (1.34)	5.4 (0.24)	3.6 (0.16)	0.2 (0.01)	13.0 (0.58)	5.1 (0.23)
1990	37,399	1,743	4.66	33.6 (1.57)	33.2 (1.55)	4.8 (0.22)	3.5 (0.16)	0.1 (0.00)	20.7 (0.96)	4.1 (0.19)
1991	35,618	1,350	3.79	33.7 (1.28)	34.7 (1.32)	4.7 (0.18)	3.6 (0.13)	0.0 (0.00)	19.2 (0.73)	4.1 (0.16)
1992	33,201	1,177	3.55	36.3 (1.29)	37.3 (1.32)	5.4 (0.19)	4.2 (0.15)	0.0 (0.00)	12.3 (0.44)	4.4 (0.16)
1993	31,207	1,136	3.66	37.2 (1.36)	36.5 (1.34)	4.5 (0.16)	3.4 (0.12)	0.3 (0.01)	14.5 (0.53)	3.5 (0.13)
1994	27,827	882	3.17	35.5 (1.12)	40.7 (1.29)	6.1 (0.19)	3.2 (0.10)	0.1 (0.00)	10.4 (0.33)	4.0 (0.13)

[a] An unidentified fungus was observed in the infected organ.
[b] Mixed infection with more than two kinds of fungi in the infected organ.

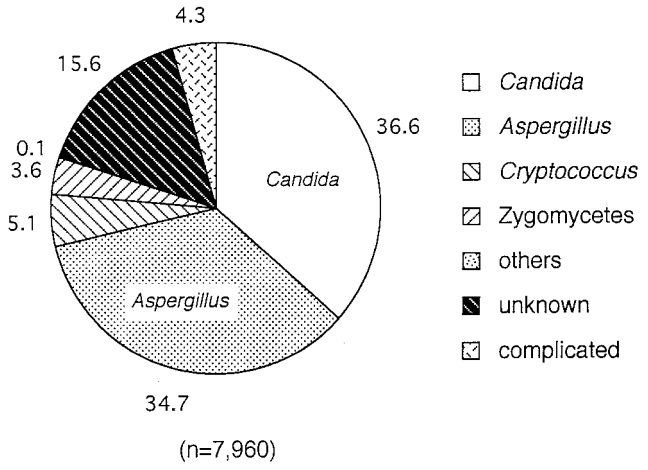

FIG. 2. Causative agents for visceral mycoses in autopsy cases. Data were from references 32 to 37. Each agent is reported as a percentage of the total mycoses (7,960 cases).

TABLE 2. Distribution of causative agents of mycoses by organ[a]

Infection type or organ	% of infections caused by:			
	Candida (n = 2,172)	*Aspergillus* (n = 1,967)	*Cryptococcus* (n = 289)	Zygomycetes (n = 209)
Total	100.0	100.0	100.0	100.0
Systemic	16.7	8.6	13.5	9.6
Fungemia	13.7	4.3	4.8	5.3
Brain + meninx	4.1	3.3	21.5	5.3
Mouth + tongue	2.2	0.3	0.0	0.0
Esophagus	15.9	1.3	0.7	0.5
Stomach	11.1	2.9	0.3	7.2
Intestine	8.0	2.6	0.0	4.8
Liver	8.1	3.6	3.5	9.6
Larynx + pharynx	1.2	0.3	0.0	0.0
Lung + bronchia	34.7	83.9	64.0	69.4
Heart	13.4	7.4	3.8	7.7
Kidney	23.3	7.3	9.7	9.1
Bladder	3.5	0.5	0.0	0.0
Thyroid	3.5	3.5	2.4	3.3
Spleen	3.7	2.2	6.2	6.2
Other	11.9	5.8	10.0	14.4

[a] Data were compiled from references 32, 33, 34, and 36.

visceral mycoses among the annual total number of autopsy cases increased significantly, from 1.60% in 1969 to a peak of 4.66% in 1990. After 1990, however, this frequency decreased gradually, from 3.79% in 1991 to 3.17% in 1994. Candidiasis also increased, from 0.41% in 1969 to a peak of 1.89% in 1989, and then decreased to 1.12% by degrees after 1991. In contrast, the aspergillosis rate rose from 0.39% in 1969 to a peak of 1.55% in 1990 and maintained a constant level of about 1.3% after 1991. The rate of zygomycosis increased slowly (from 0.01 to 0.16%), whereas that of cryptococcosis was not remarkably changed (from 0.14 to 0.26%) during that time. Until 1989, the predominant causative agent was *Candida*, followed by *Aspergillus* and *Cryptococcus* in that order. Although the rate of candidiasis decreased by degrees from 1990, the rate of aspergillosis increased up to and then surpassed that of candidiasis in 1991.

A comparison of the causative agents of mycoses over the 6 years preceding 1994 showed that *Candida* was the most common causative agent, with 36.6% of the total of 7,960 cases, followed in order by *Aspergillus* (34.7%), *Cryptococcus* (5.1%), and Zygomycetes (3.6%) (Fig. 2). Table 2 lists the organ distribution of these causative agents. In candidiasis, the lung and bronchial system constituted the most frequently involved site, with 34.7% of the total candidiasis cases, followed by the kidney (23.3%). Esophagus, heart, and stomach infections also occurred at high frequencies (15.9, 13.4, and 11.1%, respectively). High rates of systemic candidiasis (16.7%) and candidemia (13.7%) were also observed. For aspergillosis, the lung and bronchia comprised the most commonly infected organ system (83.9%); other organs were not involved at a high rate. *Cryptococcus* also infected the lungs and bronchia most frequently (64%), followed by the brain and meninx (21.5%). Zygomycosis was also observed most commonly in the lung and bronchia (69.4%), followed by the liver (9.6%) and kidney (9.1%).

When the data on diseases underlying the visceral mycosis cases for the years from 1989 to 1991 and 1993 were compiled, among a total of 5,901 cases, leukemia and myelodysplastic syndrome (MDS) were the major diseases (25.5%), followed by solid cancers (25.1%) and other blood and hematopoietic system diseases not including leukemia (15.5%). When the total number of cases of blood and hematopoietic system diseases, including leukemia, malignant lymphoma, aplastic anemia, and multiple myeloma, etc., was compared with that of solid cancers, they were found to comprise over 40% of all underlying diseases and to be 1.6 times more frequent than solid cancers.

Furthermore, when the frequencies of mycoses in each of these major underlying diseases were compared in more detail over the same periods, higher frequencies were observed in pharyngeal (2.7%), ovarian (2.6%), bladder (2.6%), and lung (2.4%) cancers among the patients with solid cancers (Table 3). Among the patients with blood and hematopoietic system diseases, the highest frequency of mycosis was observed for chronic myeloid leukemia (43.6%), followed by acute lymphatic leukemia (42.8%) and acute myeloid leukemia (35.4%) (Table 3). Mycotic infections occurred at a more-than-10-times-higher frequency in leukemia patients than in solid-cancer patients (24.8 and 1.7%, respectively). Among AIDS patients, about 23% had suffered from mycoses (Table 3). In the comparison of causative mycotic agents for the four major underlying diseases and solid-organ transplantation cases (Table 4), aspergillosis was the most predominant, followed in order by candidiasis, zygomycosis, and cryptococcosis, for leukemia; however, for the others, candidiasis was the most frequent disease, followed by aspergillosis and cryptococcosis. In contrast, mycoses among organ transplant patients were reported in only 10 cases during this period.

Most systemic or multiorgan mycotic infections caused patients to die in a short period, responded poorly to currently available antifungal agents, or required a long period of treatment. The frequency of such severe mycotic infections has increased dramatically over the 25-year study period, from 6.6% of the total visceral mycosis cases in 1969 to 71.3% in 1994 (Fig. 3).

When the proportions of causative agents for the severe mycoses were compared for the years 1989 and 1994, candidiasis (41.1%) was found to be the most frequent mycosis, followed by aspergillosis (28.5%), in 1989, but aspergillosis (44.5%) surpassed candidiasis (27.7%) in 1994 (Fig. 4).

Analysis of the frequency of severe infections for each causative agent showed that 93% of zygomycosis, 83% of cryptococcosis, 78% of aspergillosis, and 56% of candidiasis cases

TABLE 3. Details for each category of underlying disease[a]

Disease type	Site or diagnosis[b]	Total no. of patients	No. (%) with mycosis
Solid cancers	Lung	15,340	369 (2.4)
	Stomach	12,719	227 (1.8)
	Liver	13,985	167 (1.2)
	Pancreas	5,046	100 (2.0)
	Colon	7,140	82 (1.1)
	Esophagus	3,124	58 (1.9)
	Gall bladder	3,478	67 (1.9)
	Breast	2,274	37 (1.6)
	Uterus	2,068	40 (1.9)
	Prostate	3,278	29 (0.9)
	Ovary	1,248	32 (2.6)
	Kidney	2,110	38 (1.8)
	Bladder	1,590	41 (2.6)
	Brain	1,824	37 (2.0)
	Thyroid	3,005	15 (0.5)
	Pharynx	752	20 (2.7)
	Total	78,981	1,359 (1.7)
Blood and hematopoietic system diseases	AML	1,753	620 (35.4)
	CML	424	185 (43.6)
	ALL	745	319 (42.8)
	CLL	119	17 (14.3)
	MoL	278	49 (17.6)
	MDS	473	105 (22.2)
	ATL	535	116 (21.7)
	Other leukemia	1,740	95 (5.5)
	Total for leukemia and MDS	6,067	1,506 (24.8)
	Malignant lymphoma	4,649	487 (10.5)
	Multiple myeloma	1,834	170 (9.3)
	Aplastic anemia	388	103 (26.5)
	DIC	1,761	18 (1.0)
	Purpura	130	12 (9.2)
	Immunological disorders	52	10 (19.2)
	AIDS	109	25 (22.9)
	Total for other blood and hematopoietic system diseases	8,923	825 (9.2)
	Total	14,990	2,331 (15.6)

[a] These data were taken from references 32, 33, 34, and 36. Among 78,981 patients with solid cancers, 1,359 patients suffered from mycoses. The mycosis rate for the solid-cancer patients was 1.7%. For blood and hematopoietic system diseases, 1,506 mycosis patients were among 6,067 leukemia and MDS patients (24.8%), and 825 patients, excluding leukemia and MDS patients, suffered from mycoses among 8,923 other patients with blood and hematopoietic system diseases (9.2%). In total, 15.6% of patients with blood and hematopoietic diseases suffered from mycoses.

[b] AML, acute myeloid leukemia; CML, chronic myeloid leukemia; ALL, acute lymphatic leukemia; CLL, chronic lymphatic leukemia; MoL, monocystic leukemia; ATL, adult T-cell leukemia; DIC, disseminated intravascular coagulation syndrome; Purpura, idiopathic thrombocytopenic purpura or thrombotic thrombocytopenic purpura.

were found among the severe cases in 1994. That rate for each agent was almost exactly 50% in 1989.

By age, the highest frequency of mycoses was observed in patients in their 20s, whereas the highest incidence was observed in those in their 60s and 70s. In 1993 and 1994, neonatal babies showed a tendency to suffer from candidiasis, which might be caused by endogenous pathogens (Table 5).

TABLE 4. Causative agents of mycoses with the major underlying diseases[a]

Agent	Leukemia and MDS		Solid cancers[b]		Lymphoma		Myeloma		Organ transplantation	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Candida	397	26.4	713	48.0	178	36.6	64	37.6	3	30.0
Aspergillus	564	37.5	377	25.4	151	31.0	50	29.4	2	20.0
Cryptococcus	25	1.7	90	6.1	19	3.9	13	7.6	2	20.0
Zygomycetes	101	6.7	23	1.5	17	3.5	12	7.1	0	0.0
Other	5	0.3	2	0.1	1	0.2	0	0.0	0	0.0
Unknown	296	19.7	246	16.6	102	20.9	23	13.5	2	20.0
Complicated	118	7.8	34	2.3	19	3.9	8	4.7	1	10.0
Total	1,506	100.0	1,485	100.0	487	100.0	170	100.0	10	100.0

[a] Data are from references 32, 33, 34, and 36.

[b] Solid cancers include the cases listed in Table 3 plus 126 other cases.

There was no remarkable difference between the sexes in the frequency of visceral mycoses in total autopsies as determined from the 1993 and 1994 compiled data (36, 37). There was little difference in candidiasis between men and women (1.21 and 1.31%, respectively); cryptococcosis was found at a higher frequency in women than in men (0.29 and 0.13%, respectively) in total autopsy cases, whereas aspergillosis was found slightly more frequently in men (1.39%) than in women (1.18%). The frequencies of mycoses in both sexes relative to total autopsies were almost the same (3.4%).

DISCUSSION

Candidiasis is the most common mycotic disease in Japan, requiring the treatment of 73,000 patients (ca. 6,000 male and ca. 68,000 female) who received medical treatment in hospitals or clinics in 1993 (51). The most frequently presented symptoms were of *Candida* vaginitis in women in their 20s and 30s; however, very few of the visceral-candidiasis patients succumbed to the disease. Figure 1 shows the frequency of candidiasis that had been certified as a direct cause of death. It appears that even if a patient suffers from a mycosis and dies from that mycosis, in the presence of an underlying disease, the

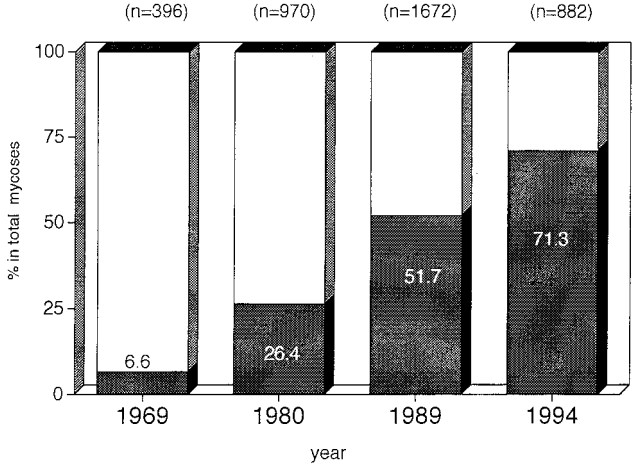

FIG. 3. Increase in the proportions of severe infections for all mycoses. (Data are from references 18, 29, 32, and 37.) Frequencies of severe mycoses for the 25-year period were compared. ▨ severe infection; ▭, nonsevere infection. Severe mycoses increased dramatically, from 6.6% in 1969 to 71.3% in 1994.

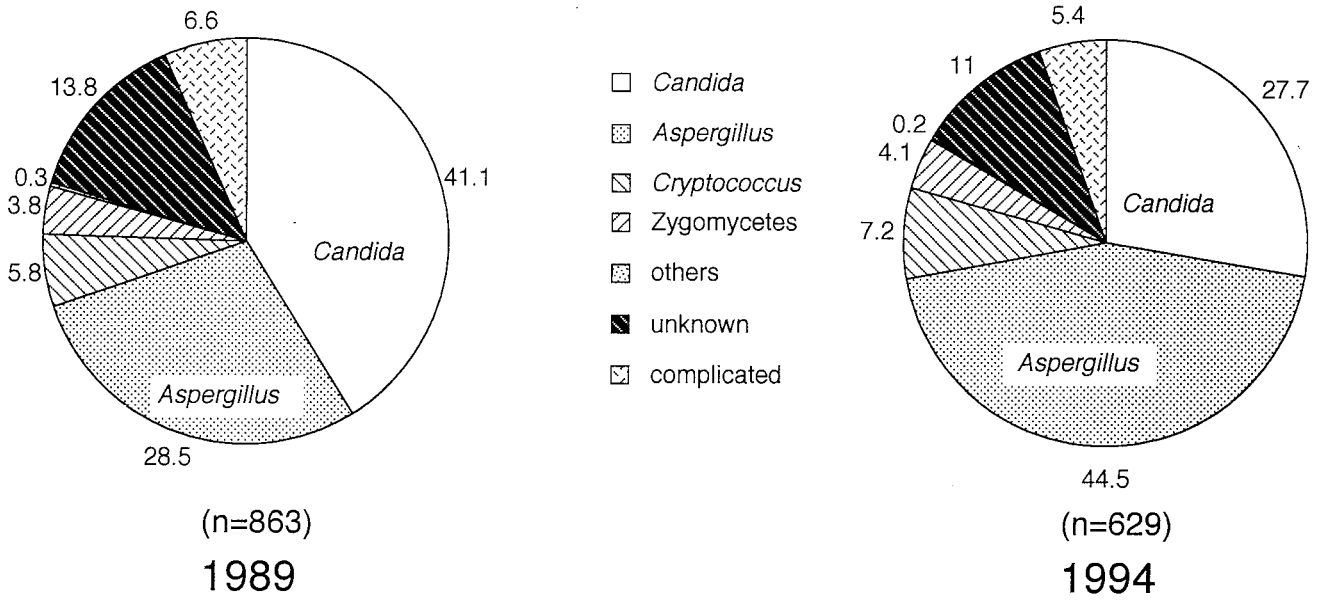

FIG. 4. Comparison of the proportions of causative agents for severe mycoses in 1989 and in 1994. Each agent is reported as a percentage of total mycoses. Severe candidiasis cases decreased but aspergillosis cases increased in 1994.

direct cause of death might be certified as being the major cause because of difficulty in making the diagnosis.

In this epidemiological and etiological study, the retrospective autopsy data that we used were compiled by the Japanese Society of Pathology from data gathered from university hospitals, public hospitals, and large private hospitals all over Japan. Visceral mycoses continued to increase up to 1990; however, their frequency has been decreasing since 1991. Especially, candidiasis cases have tended to decrease after 1989. In contrast, aspergillosis cases had increased by 1990, and that frequency was constant at 1.3% of total autopsy cases from 1990 to 1994. Groll et al. had also reported almost the same trend for the increase of aspergillosis in their pathological autopsy data obtained in Frankfurt, Germany (14, 15). The major reason for this turnaround in our data is thought to be the introduction of fluconazole in Japan. Fluconazole treatment has likely decreased the cases of both severe and nonsevere *Candida* infections; however, its activity against aspergillosis should be limited (1, 6, 41). Kujath and Lerch reported their clinical experience in treating *Aspergillus* infections of multiple soft-tissue injuries, which did not improve under treatment with fluconazole (300 mg daily for 16 days) (41). Anaissie et al. also reported that one patient with pneumonia due to *Aspergillus glaucus* responded partially to fluconazole at 2,000 mg/day but that three patients did not respond to high-dose fluconazole treatment (more than 800 mg/day) (1). Thus, they concluded that the activity of fluconazole was limited in severe infection with *Aspergillus* species and other molds.

The introduction of fluconazole in the middle of 1989 was a kind of turning point against candidiasis (11, 17, 44) but not against other severe mycoses such as invasive aspergillosis. Itraconazole was introduced in 1993; however, the effect of itraconazole on clinical outcomes might not be evident within this surveyed period. When the causative agents for 1989 and 1994 were compared, we could see that the predominant causative agent for severe mycotic infection had shifted from *Can-*

TABLE 5. Frequencies and incidences of the visceral mycoses by age[a]

Age (yr)	Total no. of autopsy cases	Total mycoses		*Candida*		*Aspergillus*		*Cryptococcus*		Zygomycetes		Other		Unknown		Complicated	
		n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Neonatal babies	1,491	23	1.54	18	1.21	0	0.00	0	0.00	0	0.00	0	0.00	5	0.34	0	0.00
0–9	1,324	40	3.02	17	1.28	12	0.91	0	0.00	2	0.15	0	0.00	7	0.53	2	0.15
10–19	532	52	9.77	14	2.63	25	4.70	0	0.00	4	0.75	0	0.00	6	1.13	3	0.56
20–29	836	84	10.05	36	4.31	34	4.07	2	0.24	5	0.60	0	0.00	6	0.72	1	0.12
30–39	1,203	84	6.98	29	2.41	31	2.58	5	0.42	5	0.42	0	0.00	11	0.91	3	0.25
40–49	3,942	156	3.96	39	0.99	75	1.90	10	0.25	5	0.13	0	0.00	20	0.51	7	0.18
50–59	8,169	312	3.82	105	1.29	120	1.47	14	0.17	10	0.12	2	0.02	47	0.58	14	0.17
60–69	16,385	544	3.32	192	1.17	209	1.28	27	0.16	18	0.11	1	0.01	75	0.46	22	0.13
70–79	15,561	537	3.45	194	1.25	220	1.41	30	0.19	11	0.07	1	0.01	62	0.40	19	0.12
≥80	9,567	186	1.94	92	0.96	48	0.50	17	0.18	7	0.07	0	0.00	18	0.19	4	0.04
Total	59,010	2,018	3.42	736	1.25	774	1.31	105	0.18	67	0.11	4	0.01	257	0.44	75	0.13

[a] The highest frequency of mycoses was observed for individuals in their 20s, whereas the highest incidence was in those in their 60s and 70s. Neonatal babies showed a tendency to suffer from candidiasis due to an endogenous pathogen. These data were taken from references 36 and 37.

dida to *Aspergillus* (Fig. 4), and the proportion of severe infections among the total mycoses had increased from 6.6% in 1969 to 71.3% in 1994 (the most recent data) (Fig. 3).

We can guess that the reasons for this decrease of candidiasis combined with an increase of aspergillosis or of other severe mycotic infections might be that (i) antifungal-responsive (not disseminated) infections were excluded from the case totals, because they have become controllable by antifungal drugs such as fluconazole (launched in the middle of 1989 in Japan); (ii) an empirical therapy was commonly given to prevent immunocompromised patients from acquiring primary mycoses; (iii) available antifungal drugs were partially efficacious for severe infections; (iv) diagnostic techniques for both candidiasis and aspergillosis were inadequate and not yet fully developed (12, 40, 52, 53, 55); or (v) the number of patients living longer in an immunocompromised state increased as a result of developments in chemotherapy, organ transplantation, and bone marrow transplantation (BMT).

Until 1994, kidney transplantation was not uncommon, even in Japan, but liver transplantation was only starting to be done. BMT was very rare at that time. Therefore, we could not derive the number of mycoses after BMT from available reports of pathological autopsy cases up to 1994.

Even though the number of solid organ transplantation cases is increasing, BMT is still not a common procedure in Japan. Also, AIDS patients were rare in Japan more than 5 years ago. In contrast, many AIDS patients have been diagnosed with mycoses in the United States and European countries (9, 13, 15). In fact, 20% of patients suffering from AIDS have been reported to have mycotic infection as one complication (Table 3). Even now, cases of severe visceral mycoses are essentially uncontrollable, and their numbers are still increasing (4, 8, 15, 54). Therefore, there is an urgent, unmet medical need for drugs that are highly potent against visceral mycoses and have efficacy against aspergillosis, azole-resistant *Candida* stains, or non-*C. albicans Candida* species as well as other mycoses.

With respect to the affected-organ distribution data (Table 2), the rate of candidemia was higher than that of fungemia from *Aspergillus*, *Cryptococcus*, or Zygomycetes. The increasing use of indwelling intravenous catheters might be one major infection route for fungemia, and *Candida* as an endogenous pathogen is more easily infective than other pathogens. Unfortunately, we could not find any available data on the incidence of candidemia to be compared with data for autopsy trends.

We observed a difference in the organ distribution among the causative agents: the lung and bronchial system were most frequently involved regardless of the pathogen species. This suggests that the lung and bronchia are at the highest risk of being exposed to not only exogenous pathogens, such as *Aspergillus*, *Cryptococcus*, or Zygomycetes, but also *Candida* species. Although *Candida* species are normally found commensally in the digestive tract, it is possible for them to be a major causative agent of systemic infection in immunocompromised patients and of topical infections in healthy individuals. Further, such *Candida* is known to be involved in nosocomial transmission (2). That might explain why the lung and bronchia are found to be the organs predominantly infected by *Candida*. Reasonably, *Candida* infections were also observed more commonly than those of the other three major species in the esophagus and stomach.

The data from autopsy surveys include both patients of antemortem-diagnosed cases and those recognized by postmortem necropsy. The former cases include those not completely cured at the time that death occurred from the underlying disease or the mycosis. In Japan, only about 3% of bodies are subjected to pathological autopsy. We assume that even if we were able to analyze all patients who died from disease, the frequency of mycotic infection would probably not change much statistically. If we could count all mycosis patients regardless of their good or bad convalescence, however, the rate of mycoses would probably be greatly different from the result that we arrived at in this study. This is because most of the data on mycoses obtained at autopsy must be biased toward those patients who had died from malignant diseases.

Almost all systemic fungal infections, especially those caused by *Aspergillus* or Zygomycetes, in immunocompromised patients are refractory to all antifungal agents currently available, even though effective drugs do exist for less severe or locally limited infections. We could expect, however, that many such patients could be cured of or prevented from contracting systemic mycoses with aggressive effective treatments.

Despite the limitations inherent in individual autopsy data in Japan, they are still worthy of use to gain much epidemiological and etiological information. Nevertheless, further information could be derived by using newer data, as they become available, and other means of analysis.

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