Esophageal Candidiasis

Kazunori HOSHIKA and Mitsuo IIDA

Division of Gastroenterology, Department of Medicine, Kawasaki Medical School, Kurashiki 701-0192, Japan

Accepted for publication on January 14, 1998

ABSTRACT. *Candida* infection is now a major problem in the increasing immunocompromised population. Esophageal candidiasis, however, occurs mainly in three conditions; an immunocompromised state (leukemia, aquired immune deficiency syndrome), a fungi overgrowth state (long term administration of antibiotics), and a non-immunosuppressive state (healthy individuals). This condition presents most commonly with dysphagia, a feeling of obstruction on swallowing and substernal pain, alone or in combination. A double-contrast radiograph of the esophagus reveals shaggy mucosal irregularities, nodular filling defects and ulcerations. The characteristic endoscopic appearance of esophageal candidiasis is yellow-white plaques, scattered in the esophagus or covering the whole esophagus. We emphasize that the diagnosis of this condition should depend on mycological and histopathological evidence. Esophageal candidiasis is a condition that can be diagnosed with scientific confidence from histological proof of candidial tissue invasion in biopsy material from a lesion. Nystatin, fluconazole and amphotericin B have often been used successfully to treat this condition.

Key words: esophagus — candidiasis

The prevalence of candidiasis in the gastrointestinal tract has been established post mortem, with esophageal involvement being seen in 28-56% of cases, and gastric involvement in 23-35%.[1-4] The esophagus is a common site of *Candida* infection in the gastrointestinal tract and lesions of other parts of the gut are seen far less often.

Prior to the 1950s, esophageal candidiasis used to be seen in infants,[5] and it was one of the important causes of infant death.[6] Improvements in the antifungal treatment of thrush in infancy have produced apparent changes in the incidence of esophageal candidiasis in different patient groups. In the 1960s, a high prevalence of esophageal candidiasis among patients with hematological malignancies was reported.[1,6-8] Now, *Candida* infection, especially nosocomial infection, is now a major problem in the increasing immunocompromised population.[9]

At present, it is well known that esophageal candidiasis occurs mainly in three conditions.[10] *Candida* infection occurs as an opportunistic infection in immunocompromised hosts such as patients with leukemia, organ transplant patients, or those with aquired immune deficiency syndrome (AIDS). Esophageal candidiasis also occurs in patients experiencing long-term administration of antibiotics and in patients with diabetes mellitus, and the mechanisms of these *Candida* infections appear to involve overgrowth of

星加和徳，飯田三雄

Candida albicans, which leads to invasive infection under these conditions. Although the mechanisms of infection have not yet been clarified, esophageal candidiasis has furthermore been reported recently in healthy individuals.[11,12]

INCIDENCE

The case rate of esophageal candidiasis has ranged from 0.1% to 0.2% among autopsy cases,[3] the prevalence among cancer patients has ranged from 2.8% to 6.7%,[1,6–8] and the case rate among all patients examined by endoscopies has ranged from 1 to 7%.[13,14]

There has been evidence of changes in trends of incidence of esophageal candidiasis. The condition is so prevalent among AIDS patients[15] that this disease must be now considered a major setting for esophageal candidiasis in the world, although esophageal candidiasis with AIDS is not yet common in Japan.

ETIOLOGY/PATHOGENESIS

Candida albicans is the major species in esophageal candidiasis, although a high prevalence of *Candida tropicalis* has been reported in some studies.[16] Although the gastrointestinal tract can be infected by *Candida albicans* from its mucosal surface or via the bloodstream, in most cases, mucosal invasion seem to be most common.

At present, it is well known that esophageal candidiasis occurs mainly in three conditions; an immunocompromised state (leukemia, AIDS), a fungi overgrowth state (long-term administration of antibiotics), and a non-immunosuppressive state (healthy individuals). In addition to the frequent occurrence of esophageal candidiasis in immunocompromised hosts, esophageal candidial lesions have been usually observed in animals treated with immunosuppressive drugs and in genetically immunocompromised hosts in experimental studies. Therefore, an immunodeficient state has been considered necessary for the formation of candidial lesions. However, since esophageal candidiasis has been also recognized in non-immunocompromized hosts, previous hypotheses of *Candida* infections must be reconsidered, and a new concept of *Candida* infections is required.

There has been little study of the mechanisms of adherence to the esophagus as the first step of *Candida* infection, despite the fact that the esophagus is the most common site of *Candida* infection in the gastrointestinal tract. Our in vitro studies on the adherence of *Candida albicans* to the squamous epithelium of the esophagus, using a scanning electron microscope, demonstrated that this adherence can be classified into four modes; attachment, subepithelial cell insertion, cavitation and invasion.[17] Subepithelial cell insertion is the characteristic adherence mode of the esophagus, and consists of the wedging of *Candida albicans* cells under the edges of epithelial cells. In addition, our research has suggested that physical contact of *Candida albicans* with the esophagus leads to its adherence by the modes of attachment and/or subepithelial cell insertion, and can lead to the development of candidial lesions in the esophagus in a nonimminosuppressed state.[18] We tested our hypothesis by experiments in vivo and succeeded in creating candidial lesions

by establishing repeated physical contact of *Candida albicans* with the esophageal epithelium without the use of immunosuppressive drugs and/or antibiotics. This condition may be presumed to be that of healthy individuals. The successful induction of *Candida* infection without the use of immunosuppressive drugs in the mouth of the mouse[19] supports our hypothesis. In addition, minute candidial lesions, which were too small to detect macroscopically, were observed in rabbits given suspensions of *Candida albicans* for various periods. The results suggest that cumulative micro-*Candida* infections exist in non-immunocompromised hosts and that these infections may be the first step of infection in all three conditions. Although the wide spectrum of candidiasis conditions, ranging from superficial to invasive, may not be caused by a single factor, secreted asparatic proteinase produced by *Candida dlbicans* may be one of the important pathogenic mechanisms in invasive infection.[20]

CLINICAL FEATURES

Esophageal candidiasis presents most commonly with dysphagia, a feeling of obstruction on swallowing and substernal pain, alone or in combination. Fever, vomiting, hematemesis, epigastric pain and other thoracic symptoms are also seen in some cases. However, no presenting symptoms are noted in a majority of patients with mild esophageal candidiasis. In patients with AIDS, the infection is also silent or may present in unusual ways.[21]

Esophageal candidiasis may occur by direct extension of oral candidiasis, but patients with this disease have not always had oral candidiasis.[22,23] Furthermore, the esophagus has usually been the only site involved, and more often in the distal rather than the proximal part of the esophagus. Patients with esophageal candidiasis are usually older than 50 years : relatively few are younger than 30. It is also important to recognize that esophageal candidiasis can occur simultaneously with herpes simplex virus esophagitis or cytomegalovirus esophagitis in severely immunocompromised patients.[24]

DIAGNOSIS

X-ray features

Radiological changes in mild esophageal candidiasis may be inapparent.[25] Double-contrast radiographs of the esophagus have revealed shaggy mucosal irregularities and nodular filling defects.[25,26] With increased severity of the disease, a nodular pattern becomes extensive, resulting in an appearance variously described as resembling cobblestones or snakeskin. Esophageal ulceration and stenosis are features in severe cases. Intramural pseudodiverticulosis is rarely associated with this condition.

Endoscopic features

The characteristic endoscopic appearance of esophageal candidiasis is yellow-white plaques, scattered in the esophagus or covering the whole esophagus (Fig 1).[24] However, white plaques in the esophagus are not exclusive to *Candida* infection.[27] Ulcerations are associated with progressive infection, but they may be missed endoscopically when they are concealed by

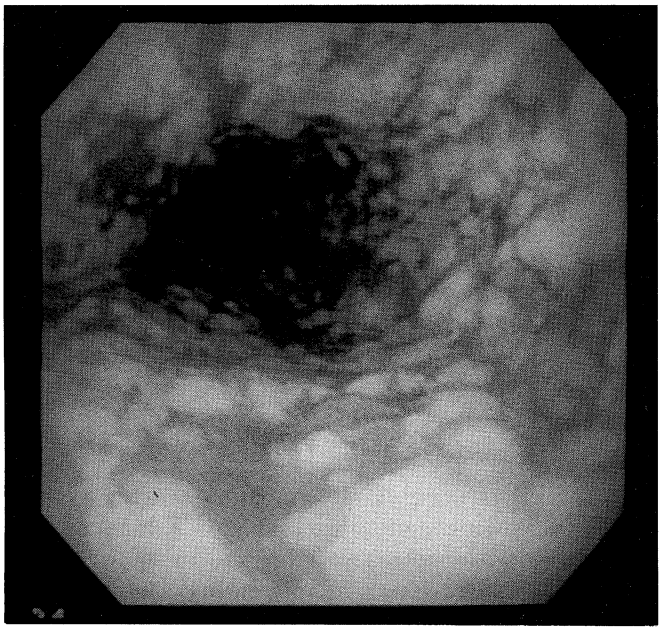

Fig 1. Endoscopic examination discloses esophageal candidiasis with yellow-white plaques covering the whole esophagus.

candidial plaques.[28]

Endoscopic appearance may be graded as follows[13]: grade I, a few raised white plaques up to 2 mm diameter with hyperemia, but no ulceration; grade II, multiple raised plaques greater than 2 mm diameter with hyperemia, but no ulceration; grade III, confluent, linear and nodular elevated plaques with hyperemia and frank ulceration; grade IV, grade III with increased friability of the mucosa and occasional narrowing of the lumen.

Serological tests

Serological tests may show circulating *Candida* antigen[29] or rises in the antibody titre[30] in patients with esophageal candidiasis, but such findings are not specific diagnostic indicators of the condition and are therefore of limited assistance in establishing a diagnosis, because *Candida* species exist in the esophagus as commensals.

Mycological isolation

There have been reports of esophageal candidiasis diagnosed on the basis of only isolation of the *Candida* species or presence of *Candida* hyphae.[15] However, mere association of the presence of *Candida* species with an esophageal lesion by esophageal brushing smear, the "snowplow method"[31] or culture does not provide enough evidence to distinguish *Candida* as commensal from *Candida* as an invasive pathogen, because the presence of *Candida* together with squamous cells is just as compatible with commensal colonization as it is with invasive infaction. Therefore, isolation of the *Candida* species

from esophageal lesions does not by itself establish a diagnosis, and histological evidence is necessary for the diagnosis. Only biopsy can provide the evidence of candidial invasion.[27,32]

Recently, the polymerase chain reaction has been used to detect *Candida albicans* and molecular DNA analysis, using such method as pulse-field gel electrophoresis and contour-clamped homogenous gel electrophoresis, can provide useful epidemiological informaton.[33,34]

Histopathological evidence

Histological sections of esophageal candidiasis lesions has shown them to consist of exfoliating squamous epithelial cells with mycelial elements of *Candida albicans* cells penetrating through them, with a widened intercellular space between individual cells in the area of candidial invasion (Fig 2). Sections should be stained with periodic acid-Schiff's reagent for easy

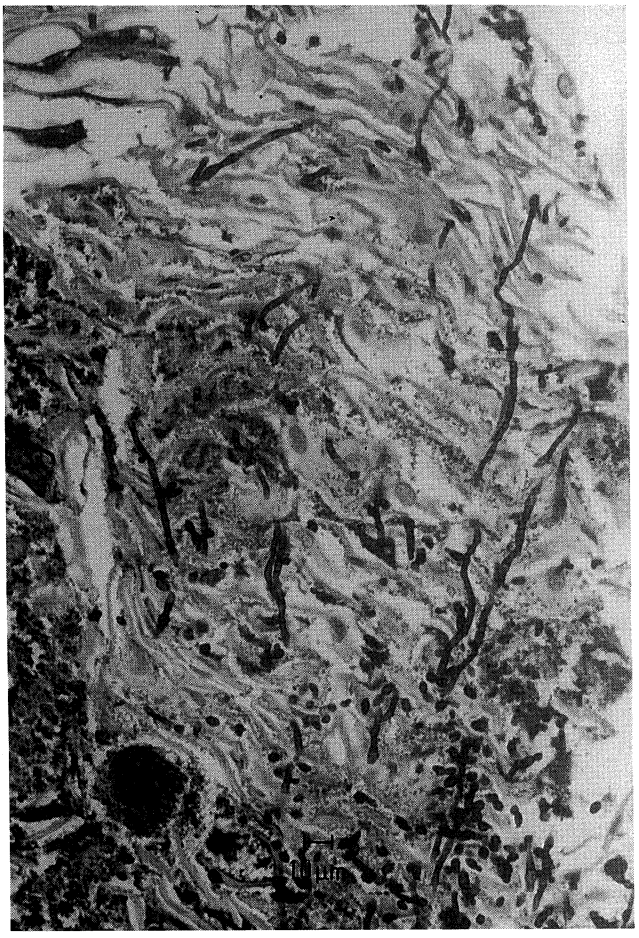

Fig 2. A histological section of a lesion from the esophageal candidiasis shows that the lesion consisted of exfoliating squamous epithelial cells with mycelial elements of *Candida albicans* cells penetrating through it. (stained with periodic acid-Schiff's reagent)

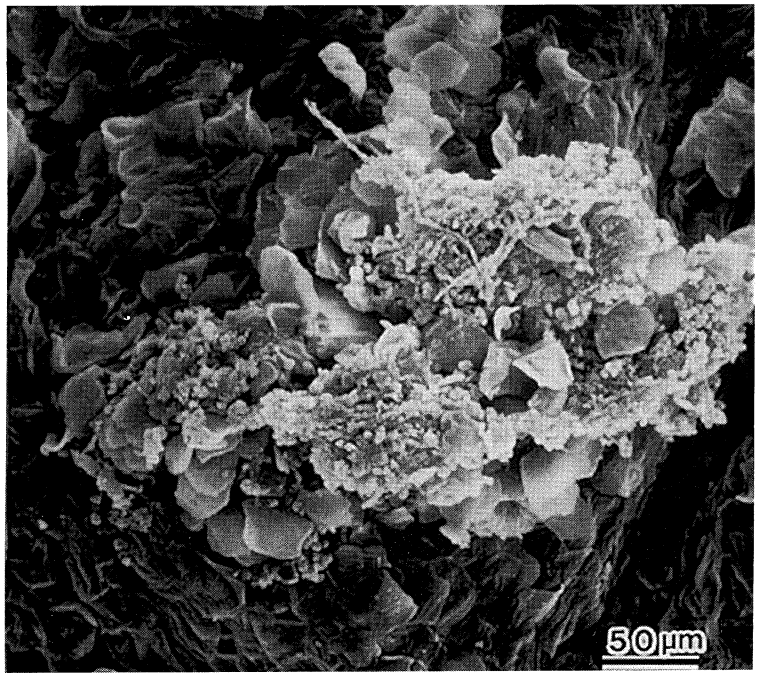

Fig 3. Scanning electron microscopic examination reveals a candidial lesion.

observation of the fungi. Bacteria have also been observed in the intercellular space between individual cells. Inflammatory cells have been observed near the mycelial invasion, and *Candida albicans* cells have been phagocytised by them.[24] Scanning electron microscopic examinations provide more easy observation of the lesions (Fig 3).

Esophageal candidiasis is a condition that can be diagnosed with scientific confidence from histological evidence of candidial tissue invasion in biopsy material from a lesion. We emphasize that the diagnosis of esophageal candidiasis should depend on both mycological and histopathological evidence.

Treatment

Esophageal candidiasis can be effectilvely treated with nystatin, fluconazole and itraconazole.[35,36] Intravenous miconazole is also effective against esophagel candidiasis.[37] When oral therapy is not effective, intravenous amphotericin B treatment may be necessary.

REFERENCES

1) Eras P, Goldstein MJ, Sherlock KT: *Candida* infection of the gastrointestinal tract. Medicine **51**: 367-379, 1972
2) Hughes WT: Systemic candidiasis: a study of 109 fatal cases. Pediatr Infect Dis **1**: 11-18, 1982
3) Kanda M, Moriyama M, Ikeda M, Kojima S, Tokunaga M: A statistical survey of deep mycoses in Japan, with particular reference to autopsy cases of cryptococcosis. Acta Pathol Jap **24**: 595-609, 1974
4) Sherlock P, Goldstein MJ, Eras P: Esophageal moniliasis. Mod Treat **7**: 1250-1260, 1970

5) Reye D: Oesophagitis of infant. Med J Aust **2**: 673-674, 1941
6) Gruhn JG, Sanson J: Mycotic infections in leukemic patients at autopsy. Cancer **16**: 61-73, 1963
7) Jensen KB, Stenderup A, Thomsen JB, Bichel J: Oesophageal moniliasis in malignant neoplastic disease. Acta Med Scand **175**: 455-459, 1964
8) Schumacher HR, Ginns DA, Warren WJ: Fungus infection complicating leukemia. Am J Med Sci **247**: 313-323, 1964
9) Cormican MG, Pfaller MA: Epidemiology of candidiasis. Compr Ther **21**: 653-657, 1995
10) Hoshika K, Iida M. Mine H: Esophageal *Candida* infection and adherence mechanisms in the nonimmunocompromised rabbit. J Gastroenterol **31**: 307-313, 1996
11) Naito Y, Yoshikawa T, Oyamada H, Tainaka K, Morita Y, Kogawa T, Sugino S, Kondo M: Esophageal candidiasis. Gastroenterol Jpn **23**: 363-370, 1988
12) Phaosawasdi K, Rice P, Lee B: Primary and secondary *Candida* esophagitis. Illinois Med J **169**: 361-365, 1986
13) Kodsi BE, Wickremesinghe PC, Kozinn PJ, Iswara K, Goldberg PK: *Candida* esophagitis: a prospective study of 27 cases. Gastroenterology **71**: 715-719, 1976
14) Young R, Elias E: Gastro-esophageal candidiasis: diagnosis by brush cytology. J Clin Pathol **38**: 293-296, 1985
15) Chandler FW: Pathology of the mycoses in patients with the acquired immunodeficiency syndrome (AIDS). Curr Topics Med Mycol **1**: 1-23, 1985
16) Walsh TJ, Merz WG: Pathologic features in the human alimentary tract associated with invasiveness of *Candida tropicalis*. Am J Clin Pathol **85**: 498-502, 1986
17) Hoshika K, Kihara T, Mine H: Adherence modes of *Candida albicans* to rabbit esophagus. J Clin Electron Microsc **25**: 261-267, 1992
18) Hoshika K, Mine H: Significance of modes of adherence in esophageal *Candida albicans*. J Gastroenterol **29**: 1-5, 1994
19) Lacasse M, Fortier C, Trudel L, Collet AJ, Deslauriers N: Experimental oral candidosis in the mouse: microbiologic and histologic aspects. J Oral Pathol Med **19**: 136-141, 1990
20) Hoegl L, Ollert M, Korting HC: The role of *Candida albicans* secreted asparatic proteinase in the development of candidoses. J Mol Med **74**: 135-142, 1996
21) Pierard GE: Unusual candidosis superimposed to pox and herpes-virus infection in a patients with AIDS. Ann Pathol **6**: 225-227, 1986
22) Grieve NWT: Monilia oesophagitis. Br J Radiol **37**: 551-554, 1964
23) Braegger CP, Albisetti M, Nadal D: Extensive esophageal candidiasis in the absence of oral lesions in pediatric AIDS. J Pediatr Gastroenterol Nutr **21**: 104-106, 1995
24) Wilcox CM, Schwartz DA: Endoscopic-pathologic correlates of *Candida* esophagitis in acquired immunodeficiency syndrome. Dig Dis Sci **41**: 1337-1345, 1996
25) Athey PA, Goldstein HM, Dodd GD: Radiologic spectrum of opportunistic infections of the upper gastrointestinal tract. Am J Roentgenol **129**: 419-424, 1977
26) Pagani JJ, Libshitz HI: Radiology of *Candida* infections. In Candidiasis, ed by Bodey GP, Fainstein V. New York, Raven Press. 1985, pp 71-84
27) Scott BB, Jenkins D: Gastro-oesophageal candidiasis. Gut **23**: 137-139, 1982
28) Wilcox CM: A technique to examine the underlying mucosa in patients with AIDS and severe *Candida* esophagitis. Gastrointest Endosc **42**: 360-363, 1995
29) Bailey JW, Sada E, Brass C, Bennett JE: Diagnosis of systemic candidiasis by latex agglutination for serum antigen. J Clin Microbiol **21**: 749-752, 1985
30) Marrier R, Andriolevt VT: Usefulness of serial antibody determinations in diagnosis of candidiasis as measured by discontinuous counterimmunoelectrophoresis using HS antigen. J Clin Microbiol **8**: 15-22, 1978
31) Ozawa S, Ohmori T, Makuuchi H, Yamazaki E, Kumagai Y: Sixty three cases of *Candida* esophagitis. Prog Dig Endosc **30**: 87-90, 1987 (in Japanese with English summary)
32) Clotet B, Grifol M, Parra O, Boix J, Junca J. Tor J, Foz M: Asymptomatic esophageal candidiasis in the acquired-immunodeficiency-syndrome-related complex. Ann Intern Med **105**: 145, 1986
33) Zervos MJ, Vazquez JA: DNA analysis in the study of fungal infections in the immunocompromised host. Clin Lab Med **16**: 73-88, 1996
34) Lin D, Lehmann PF: Random amplified polymorphic DNA for strain delineation within *Candida tropicalis*. J Med Vet Mycol **33**: 241-246, 1995
35) Laine L, Rabeneck L: Prospective study of fluconazole suspension for the treatment of oesophageal candidiasis in patients with AIDS. Aliment Pharmacol Ther **9**: 553-556, 1995

36) Barbaro G, Di Lorenzo G: Comparison of therapeutic activity of fluconazole and itraconazole in the treatment of oesophageal candidiasis in AIDS patients: a double-blind, randomized, controlled clinical study. Ital J Gastroenterol **27**: 175-180, 1995
37) Kanarek KS, Williams PR: Toxicity of intravenous miconazole overdosage in a preterm infant. Pediatr Infect Dis **5**: 486-488, 1986