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ALIMENTARY TRACT

CANDIDA ESOPHAGITIS

A prospective study of 27 cases

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A prospective study of Candida esophagitis was undertaken to determine the spectrum of this disease in a general hospital. During 1 year, in 370 consecutive endoscopies, 27 patients with Candida esophagitis were detected. The diagnosis was established by finding white plaques on endoscopy, yeast organisms on microscopic examination of a direct smear from the plaques, and a serum agglutinin titer of at least 1:160. Of these 27 patients, 14 had esophageal symptoms. Twelve patients were reendoscoped after nystatin or nystatin and flucytosine therapy. Nine patients showed absence of lesions, a negative smear, and disappearance of symptoms. Control patients had no plaques on endoscopy, no yeast organisms on microscopical examination of esophageal brushings, and a positive titer in 4 to 17% of cases. A minimal agglutinin titer of 1:160 was found in 4 to 12% of two additional groups of controls. Absence of titer precluded a diagnosis of Candida esophagitis.

Candida infection of the esophagus has been considered a relatively uncommon though specific disease entitity, suspected primarily in symptomatic patients with oral thrush or underlying debilitating diseases.[1-4] Radiological examination by barium swallow[5] and esophageal biopsy[4] have been the principal diagnostic procedures. Other endoscopic findings have been reported[1, 4] but not emphasized as a method of diagnosis. A prospective study was undertaken to determine the spectrum of Candida esophagitis at Maimonides Medical Center.

Patients and Methods

During the calendar year of 1973, there were 20,688 general hospital admissions, 688 clinic, and 775 private outpatient referrals to the Gastroenterology service. Of the patient population, 90% came from a white middle class socioeconomic background. For investigation of upper gastrointestinal symptoms, 370 patients underwent esophagogastroduodenoscopy; 267 were hospital inpatients, 47 were clinic patients, and 56 were private outpatients. The mean age of the patients was 60 years with a range of 17 to 90 years and a male to female ratio of 4:3. All patients had a complete history, physical examination, complete blood count, urinalysis, SMA 12/60 (AutoAnalyzer, Technicon Instruments Corp., Tarrytown, N. Y.) chest films, and a 12-lead electrocardiogram.

Twenty-seven patients were suspected of having Candida esophagitis by gross appearance at endoscopy. The esophagitis was graded on a scale of I to IV: grade I, a few raised white plaques up to 2 mm* in size with hyperemia but no edema or ulceration (fig. 1); grade II, multiple raised white plaques greater than 2 mm in size with hyperemia, edema, but no ulceration (fig. 2); grade III, confluent, linear, and nodular elevated plaques with hyperemia and frank ulceration (fig. 3); grade IV, finding of grade III with increased friability of the mucous membranes and occasional narrowing of the lumen (fig. 4).

The plaques were brushed, and direct smears and cultures were made from these brushings. The slides were air dried. A wet mount was prepared by adding a drop of either distilled water or 10% potassium hydroxide in the presence of excess

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* Size of the plaque is estimated by comparing it to the head of the biopsy forceps.

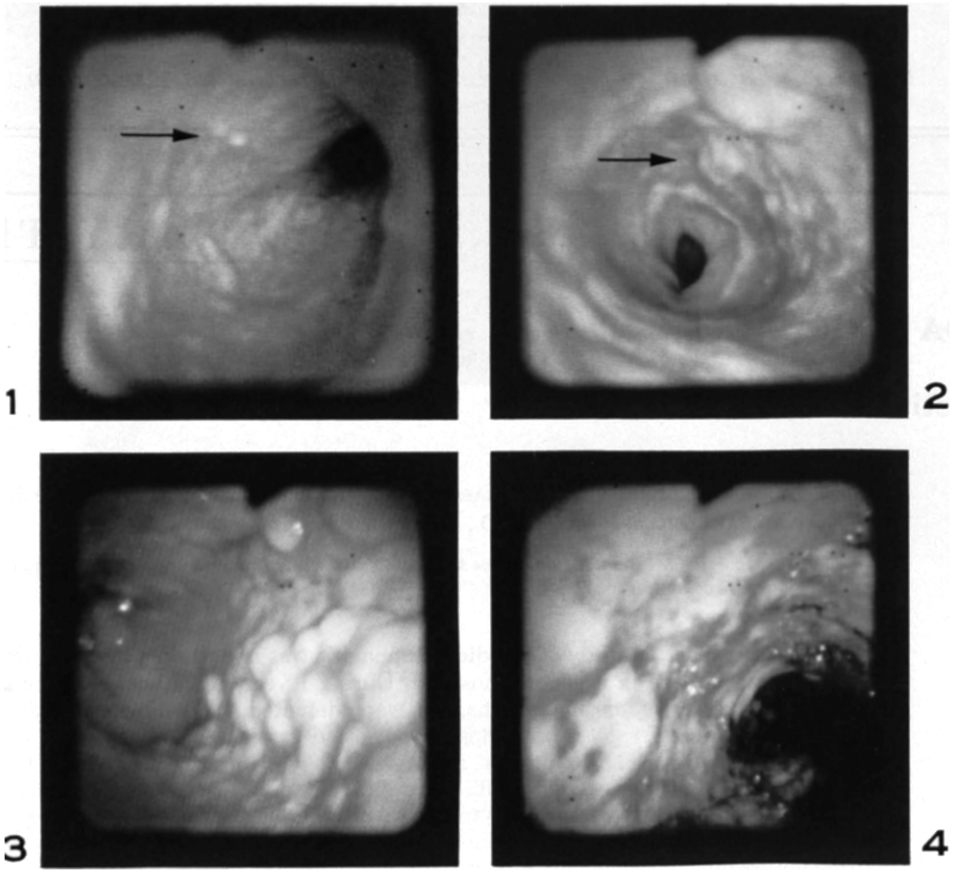

FIG. 1. Grade I Candida esophagitis.
FIG. 2. Grade II Candida esophagitis.
FIG. 3. Grade III Candida esophagitis.
FIG. 4. Grade IV Candida esophagitis.

mucus (fig. 5). Cultures were made on Nickerson's medium and the species were determined by germ tube fermentation, carbohydrate fermentation, and nitrogen assimilation techniques. The brush was first cultured to detect prior contamination with fungi. The biopsy channel was washed with soap solution and 95% ethyl alcohol after each procedure and the effluents were periodically cultured to detect the presence of fungi. A minimum of two biopsies were taken from the esophageal plaques and from the intervening areas. Histological specimens were examined after staining by hematoxylin and eosin and periodic acid-Schiff methods. Brushings, biopsies, and cultures were taken from 15 patients with the appearance of reflux esophagitis and from 18 patients with a normal-appearing esophagus.

Sera from 27 suspected cases of Candida esophagitis, 100 asymptomatic hospital employees, 164 random in-hospital patients, 18 patients with a normal esophagus at endoscopy, and 12 patients with reflux esophagitis were tested for Candida agglutinins and precipitins.[6] Quantitative serum immunoglobulins were determined in 14 of the 27 patients with Candida esophagitis.

Esophagograms were performed in 25 patients suspected to have Candida esophagitis, owing to the endoscopic appearance and mycological findings.

Twenty-four of the 27 patients were treated for 6 weeks with nystatin (Mycostatin, E. R. Squibb & Sons, Princeton, N. J.), 200,000 units, as a combined gargle and swallow every 1 to 2 hr while awake.[7] Three patients were not treated because they required emergency surgery. Four patients with persistent symptoms had supplementary flucytosine (Ancobon, Roche Laboratories, Nutley, N. J.) orally (100 mg per kg of body weight per day in four divided doses after meals for 4 to 6 weeks).[8] Weekly complete blood counts and SMA 12/60 procedures were performed to detect any untoward effects of treatment. Of 14 patients with dysphagia or odynophagia 12 were reendoscoped after treatment 1 to 6 times to evaluate the effect of therapy.

Results

Of the 370 patients who underwent endoscopy, 55 had hyperemia of the esophagus, predominantly of the lower third. Twenty-seven had elevated white plaques: 7 were classified as grade I, 12 as grade II, 6 as grade III, and 2 as grade IV Candida esophagitis (table 1). The plaques were absent in the upper third of the esophagus in all but 2 cases; 1 had oral thrush, the 2nd had no oral lesions. The patient with oral thrush suffered from acute lym-

FIG. 5. Direct smear of lesions showing Candida yeast and mycelia.

phocytic leukemia. Additional endoscopic diagnoses in the 27 patients were duodenal ulcer (6), gastric ulcer (5), erosive gastritis (4), normal upper gastrointestinal tract (4), hiatus hernia (3), atrophic gastritis (3), and partial gastrectomy (2). Direct smears and cultures from the white plaques were positive for Candida in each case. Direct smears were negative in all 15 patients with reflux esophagitis and in 18 patients with a normal-appearing esophagus; however, Candida was cultured from 6 and 12 patients, respectively. Serum Candida agglutinin titers of 1:160 or greater were present in 100% of the 27 patients with white plaques, and in 4 to 17% of four control groups (table 2). Candida precipitin titers were not helpful in the diagnosis. Serum immunoglobulins were diffusely elevated in 1 patient and normal in 13 of 14 patients studied.

The biopsies in all 27 patients with white plaques showed acute and chronic inflammatory changes. However, Candida invasion of the mucosa was seen only in 3 of the 8 patients with grade III or IV esophagitis. In the 15 patients with reflux esophagitis, the biopsies showed acute and chronic inflammation with thickening of the basal layer and the absence of Candida. The biopsies of all 18 patients with a normal-appearing esophagus were normal.

The esophagograms were reviewed by staff radiologists and one of the authors (B. K.). Findings suggestive of Candida esophagitis were absent. In the severe cases hypomotility was noted fluoroscopically and also during endoscopy.

In the 27 patients with Candida esophagitis, the male to female ratio was 3:1, the ages ranged from 24 to 82 years with a mean of 64 years. Fourteen patients had symptoms referable to the esophagus, i.e., dysphagia, odynophagia, consciousness of passage of food down the esophagus, or retrosternal pain radiating to the inter-

TABLE 1. *Correlation of the grade of Candida esophagitis with esophageal symptoms, and Candida agglutinin titers[a] in 27 patients*

Grade of esophagitis	No. of cases	Symptoms referable to the esophagus	Candida agglutinin titers		
			1:160	1:320	1:1640
I	7 (26)[b]	None	4	3	None
II	12 (44)	6 (50)	1	9	2
III	6 (22)	6 (100)	None	4	2
IV	2 (8)	2 (100)	1	1	None
Total	27 (100)	14 (52)	6 (22)	17 (63)	4 (15)

[a] Candida agglutinins in a titer of 1:160 or higher are significant.
[b] Numbers in parentheses, per cent of cases.

scapular region. Only 8 of the 27 patients had predisposing illnesses and iatrogenic factors for candidiasis: diabetes mellitus (3), acute lymphocytic leukemia (1), polycythemia vera (1), carcinoma of the esophagus (1), achalasia of the esophagus (1), and prolonged tetracycline therapy (1).

Twelve symptomatic patients treated with nystatin were reendoscoped; 8 became asymptomatic. There was a normal-appearing esophagus and a negative direct smear for Candida in 7 patients. In the 8th patient there was a diminution of the number and size of the plaques, but the direct smear remained positive. Three in this group of 7 patients gained 10, 15, and 25 pounds over a 6-month period. The 4 patients who experienced no symptomatic improvement with nystatin remained unchanged endoscopically, and the direct smear remained positive. Three of the 4 patients had underlying disease that may predispose to candidiasis. Flucytosine was then added to the nystatin treatment, and all 4 became asymptomatic. The endoscopic appearance became normal, and the direct smear became negative

TABLE 2. *Range of Candida agglutinin titers[a] in Candida esophagitis and in four control groups*

Patient groups studied	Candida agglutinin titers			
	< 1:160	1:160	1:320	1:640
A. 27 positive cases of Candida esophagitis	0	6 (22)[b]	17 (63)	4 (15)
B. 100 asymptomatic employees	96	4	0	0
C. 164 unselected hospital inpatients	144 (88)	10 (6)	6 (4)	4 (2)
D. 18 patients with a normal esophagus	15 (83)	3 (17)	0	0
E. 12 patients with reflux esophagitis	10 (83)	2 (17)	0	0

[a] Candida agglutinins in a titer of 1:160 of higher are significant.
[b] Numbers in parentheses, per cent of cases.

in 2 patients. A few plaques remained in the other 2, and the direct smear continued to be positive.

Discussion

Candida esophagitis has been recognized to be not an uncommon autopsy finding[9] particularly in oncological institutions.[3] Eras et al.[3] mentioned that this antemortem diagnosis was frequently missed in a review of 2517 autopsy protocols from an oncological institution. They found histologically proven Candida esophagitis in 45 cases. Of these, 14 had a barium study attempted within 4 weeks of deaths; 3 had abnormal esophagograms, 5 were inadequate, and 6 were normal despite the presence of severe esophagitis. In another oncological institution, Jensen et al.[1] studied 98 patients with oral thrush by endoscopy, barium swallow, and culture. They found esophagitis in 35 patients with a positive culture for Candida in all of them. The barium swallow was abnormal in 24 of the 32 patients studied. The majority of these patients were in poor condition. Moulinier et al.[4] collected 40 cases of Candida esophagitis that were diagnosed by endoscopy. They noted difficulty in demonstrating X-ray abnormalities and they were able to find yeast cells in only half of the biopsies.

The early stages of Candida esophagitis were more readily identified in this prospective study by endoscopy, direct smears, and Candida agglutinin titers. A careful, detailed history was important, inasmuch as symptoms were mild to moderate. Further, the gradation of the endoscopic appearance correlated well with the presence or absence of symptoms (table 1). A direct smear from the plaques was consistently positive for Candida, whereas a direct smear from patients with reflux esophagitis was consistently negative. In contrast, cultures for Candida were positive in both reflux and Candida esophagitis patients. Cultures are useful in determining the species and drug sensitivity but do not distinguish the pathogen from the commensal in the esophagus. A minimal agglutinin titer of 1:160 was present in every patient with the characteristic endoscopic appearance and a positive direct smear for Candida. A similar agglutinin titer was present in only 4 to 17% of four groups of controls. Such an agglutinin titer may be due to Candida infection in other organs or past infection and is, therefore, not diagnostic of Candida esophagitis. However, a titer of less than 1:160 militates against such a diagnosis.

Esophageal brushings more readily demonstrated Candida than did biopsies. Superficially situated Candida in the less severe form may be washed away in the fixing process. Biopsy sections from Candida and reflux esophagitis are indistinguishable except for the presence of Candida, which was noted in only 10% of the former.

In the absence of a predisposing illness, Candida esophagitis is mainly a disease of the elderly. Impairment of three physiological processes may play a role in the pathogenesis of the disease. The first is impaired immunity, both cellular[10] and humoral;[11] the second is impaired esophageal motility;[12] and the third is impaired carbohydrate metabolism[13, 14] associated with aging.

Candida esophagitis should always be considered in the differential diagnosis of dysphagia and odynophagia. Endoscopy, direct smear, and agglutinin titers are more valuable diagnostic aids than are the esophagogram and biopsy. Inasmuch as nystatin therapy is simple, safe, and effective, it is recommended in the treatment of Candida esophagitis.

Addendum

From January 1, 1974 to June 30, 1975, 1065 additional patients were endoscoped; 136 patients had hyperemia of the lower third of the esophagus, 61 with white plaques and 75 without plaques (reflux esophagitis). Each patient with white plaques had a positive direct smear for yeasts. Thirty of the 61 patients were tested for agglutinin titers and each had a titer of 1:160 or greater. Candida invasion was seen microscopically in 5 of 56 patients that were biopsied. All 5 had grade III or IV involvement. The upper third of the esophagus was spared in all cases except 3. Two had an underlying disease that may predispose to Candida esophagitis, chronic lymphocytic leukemia in one and a severe long standing diabetes in the other. Oral thrush was present in only these 2 patients and not in the rest of the patients with Candida esophagitis. Of 61 patients with Candida esophagitis, 30 were symptomatic. The symptoms subsided after treatment with nystatin in the 20 patients who were available for follow-up. Reendoscopy was performed in only 1 patient (grade IV) who showed modest improvement with nystatin.

Of the 75 patients with reflux esophagitis, 74 had a negative direct smear and only 1 had a positive direct smear. However, this patient was lost to follow-up and it

could not be determined whether Candida esophagitis developed subsequently. Microscopic examination of the 49 biopsies were made in the 75 patients with reflux esophagitis, showing acute and chronic inflammation and no yeasts. Agglutinin titers were done in 12 of the group; a titer of 1:160 or greater was found in 1 patient.

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