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An Observational Study of Clinical and Microbiological Profile of Esophageal Candidiasis in a Tertiary Care Center, Madras City, India

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Esophageal candidiasis, previously believed to be limited to immunocompromised individuals, is now on the rise among those with healthy immune systems. This condition can be severely debilitating, and if not managed effectively, it can lead to persistent and enduring infections.The clinical spectrum,predisposing factors and microbiological profile of esophageal candidiasis has not been evaluated previously in our hospital.

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Aim: To analyze the clinical and microbiological profile of patients with esophageal candidiasis.
Methods: The study conducted at Madras Medical College in Chennai during 2021-2022 is an observational study centered at a single institution. It involved a cohort of 100 patients diagnosed with candida esophagitis who met the specified inclusion criteria. The diagnosis of candida esophagitis (EC) in the study was established through the identification of characteristic candidal plaques during endoscopy. Biopsies were taken using standard biopsy forceps, and the diagnosis was confirmed through pathological examination, which revealed the presence of yeast forms typical for candida invading the esophageal mucosa.
Results: During the study period, around 16,000 upper endoscopies were performed in our endoscopy unit. The main findings of our study was that the prevalence of EC was less observed (0.62%, 100/16000).One fourth (26%) of our cases were presented with dysphagia followed by nausea (15%), dyspepsia (15%), asymptomatic (11%), regurgitation (9%), chest discomfort (8%), vomiting (6%), odynophagia (5%) and hiccups (5%). More than half (59%) of cases during endoscopy were grade 1 esophageal candidiasis followed by grade 2 EC (32%), grade 3 EC (8%) & oropharyngeal candidiasis observed in (1%). More than one third (39%) of cases candida lesions observed in distal esophagus followed by entire esophagus in (27%), mid esophagus in (24%) and upper esophagus in (10%). KOH mount positive in 56% cases and more than 2/3rd (67%) of EC were due to candida albicans species & one fifth (20%) showed resistance to fluconazole.
Conclusion: In conclusion, Candida esophagitis may be more common than previously suspected. Neither the presenting symptoms nor the endoscopy findings are always classic for this disease. Large-size prospective studies are needed to further identify the clinical & microbiological profile of esophageal candidiasis.

Keywords: Esophageal candidiasis; dysphagia; Fluconazole; antimicrobial; endoscopy.

1. INTRODUCTION

Candida, a yeast organism, is a normal resident of the human alimentary canal and urogenital system in healthy individuals, forming part of the natural flora. However, when the local or systemic immune system is compromised, candida overgrowth can occur, leading to candida infections [1]. There are over 15 distinct candida species that can cause diseases, with the most prevalent being C. albicans, C. glabrata, and C. tropicalis.

Commonly, mucosal candida infections affect areas such as the oropharynx, esophagus, and vagina, particularly in the general population. Among these, esophageal candidiasis stands out as a significant infection, with a high incidence in immunocompromised individuals [2,3,4,5]. Additionally, patients who have undergone treatments involving broad-spectrum antibiotics, steroids, and immunosuppressants are susceptible due to the disruption of the body's natural microflora and immune responses [6,7,8,9]. The clinical spectrum, predisposing factors and microbiological profile of esophageal candidiasis has not been evaluated previously in our hospital [10,11,12]. In this study we aim to analyze the clinical and microbiological profile of patients with esophageal candidiasis, identification of common species of candida causing candidiasis and their sensitivity patterns may help us predict response to treatment and tailor our treatment accordingly.

2. MATERIALS AND METHODS

The study is a single center observational study involving 100 patients with candida esophagitis,meeting inclusion criteria conducted at Madras medical college/Rajiv gandhi government general hospital,Chennai during the period 2021-2022.Informed consent was obtained from all individual participants included in the study.In our study, we established specific inclusion and exclusion criteria. Participants who were included in the study needed to be over 18 years of age and have a confirmed diagnosis of esophageal candidiasis through upper gastrointestinal endoscopy.On the other hand, individuals under the age of 18, those with a previous history of esophageal candidiasis, and those who declined to participate in the study were excluded from our research. A prior clearance from institutional ethics committee was obtained. EC had been diagnosed when characteristic candidal plaques were endoscopically (esophago-gastro-duodenoscopy) identified, biopsied using standard biopsy forceps by the senior faculty.Biopsy samples were aseptically collected and placed in sterile universal containers containing normal saline. Esophageal brushings were directly placed on

Sabouraud's Dextrose Agar supplemented with gentamicin (0.5 mg in 100 ml) in duplicate, and also on clean glass slides for observation under bright field microscopy. These samples were then transported to the Microbiology Laboratory.In the laboratory, a preliminary Gram staining procedure was conducted on the yeast-like growth observed, and further tests were performed to check for Germ tube and chlamydiospore formation. The preliminary identification of the isolated organisms was noted using conventional methods, and the isolates were preserved at -20°C for future reference. To screen for Candida isolates, they were cultured on CHROMagar Candida, and their identity was determined based on the color and growth pattern following themanufacturer's instructions.Automated identification and antifungal susceptibility testing were carried out. The isolated strains were tested against a range of antifungal agents, including amphotericin B, fluconazole, caspofungin, flucytosine, voriconazole, and itraconazole, to assess their susceptibility to these medications.

Clinical symptoms at the time of presentation, comorbidities, precipitating factors, indication for endoscopy, findings during endoscopy, grading of candidiasis as per Kodsi grading for endoscopic severity, site &extent, associated oropharyngeal candidiasis, complete blood count, neutrophil lymphocyte ratio, random blood sugar, ECOG performance status, KOH mount, fungal culture & drug sensitivity noted. All endoscopic examinations were performed by faculty of our hospital's gastroenterology section, using an Olympus videoscope GIF x Q 170. Candida esophagitis was diagnosed when characteristic candidal plaques were endoscopically identified and pathological confirmation of yeast forms typical for candida was found in association with an active esophagitis.

To describe the severity of candida esophagitis, a grading scale was described by Kodsi et al has been used . Candida esophagitis was graded as the following: Grade 1 as few raised lesions (<2mm) without surrounding edema or laceration, grade 2 as multiple raised lesions (>2mm) without surrounding edema or laceration, grade 3 as linear, nodular and confluent lesions, grade 4 same as grade 3 with narrowing of lumen and friability of mucosa, grade 5 as thick white plaque covering the lumen in circumferential manner causing narrowing of lumen, grade 6 as endoscopy can detect oropharyngeal candidiasis. At the time of endoscopy, routine biopsies were performed on all endoscopic abnormalities. At least 2 biopsies were performed on each esophageal lesion with standard biopsy forceps.

Data entry was accomplished using Microsoft Excel, and subsequent analysis was conducted using SPSS program version 22. The findings were presented within the text, detailing mean and standard deviation (SD) for quantitative variables, while percentages were provided for qualitative variables. To compare the mean and SD of quantitative variables across different groups, an unpaired Student's t-test was employed. For proportions or percentages among groups, the chi-square test was applied. Employing the stepwise selection method, multivariate logistic regression was employed, with a focus on variables from univariate analysis demonstrating significance at a threshold of $P < 0.01$.

3. RESULTS

During the study period, around 16,000 upper endoscopies were performed in our endoscopy unit. One hundred patients were diagnosed with candida esophagitis on the basis of endoscopic and histopathologic criteria. The age and gender distribution of esophageal candidiasis cases given in Table 1.

The clinical symptoms were dysphagia 26(26%), odynophagia 5(5%), dyspepsia 15(15%), regurgitation 9(9%), nausea 15(15%), Vomiting 6(6%), chest discomfort 8(8%), hiccups 5(5%), asymptomatic 11(11%).The comorbidities & precipitating factors for esophageal candidiasis were described in Figs 2&3.

Table 1. Age and gender distribution of esophageal candidiasis cases

		Frequency	Percentage
Age group	<50	42	42.0%
	>51	58	58.0%
Gender	F	36	36.0%
	M	64	64.0%

In cases of candida esophagitis, the severity was assessed using the Kodsi grading scale. The distribution among different grades is as follows:56(56%) cases were categorized as Grade 1,32(32%) cases were categorized as Grade 2,8(8%) cases were categorized as Grade 3, 2 (2%)cases were categorized as Grade 4, 1(1%) case was categorized as Grade 5 and 1(1%) case was categorized as Grade 6**.**The site and extent of candidiasis during endoscopy in cases were upper esophagus 10 (10%),mid esophagus 24(24%),distal esophagus 39 (39%), and pan esophagus 27(27%) described in Table 2.

The various indications for endoscopy in EC cases were described in Fig. 4.

Anemia (Hb <11 gm%) observed in 26(26%) cases, remaining 74 (74%) cases Hb level was more than 11 gm%. RBS less than 125 seen in 47 (47%) cases and more than 125 seen in 53 (53%) cases. NLR (less than 2) seen in 44(44%) cases and more than 2 seen in 56(56%) cases described in Table 3.

Fungal culture shows candida albicans in 67 (67%) cases,candida nonalbicans in 33(33%) cases and sensitive to fluconazole in 80(80%) cases,resistance to fluconazole in 20(20%) cases as described in Table 4.

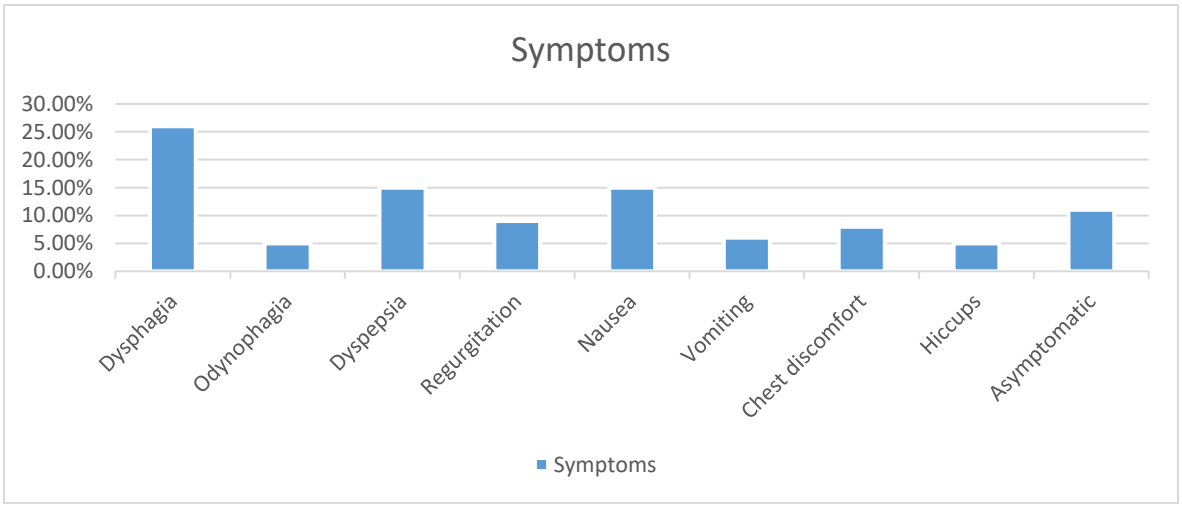

Fig. 1. Clinical symptoms of esophageal candidiasis

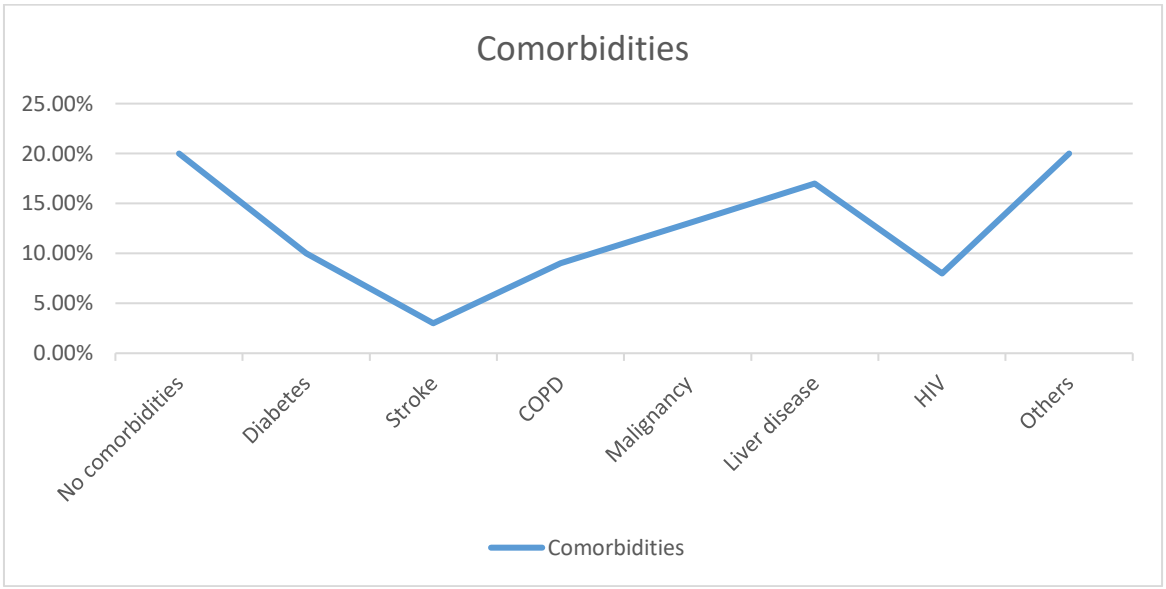

Fig. 2. Comorbidities for esophageal candidiasis

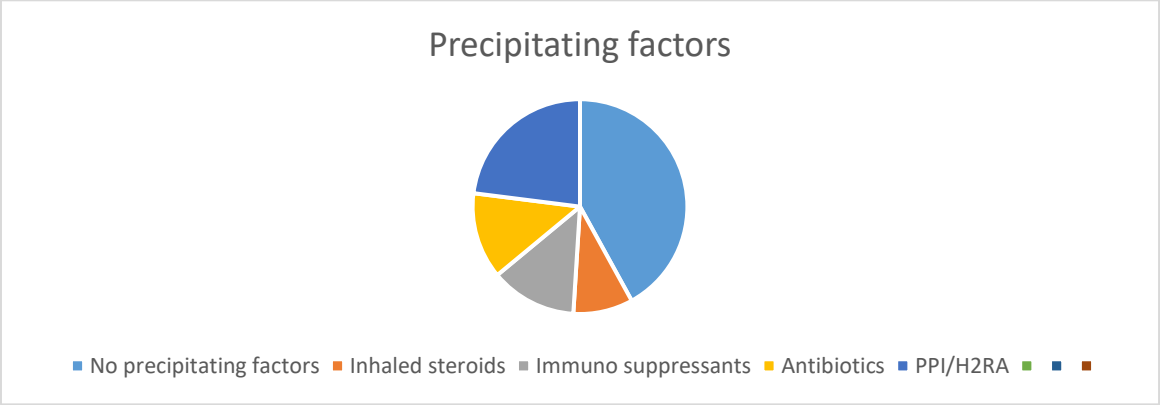

Fig. 3. Precipitating factors for esophageal candidiasis

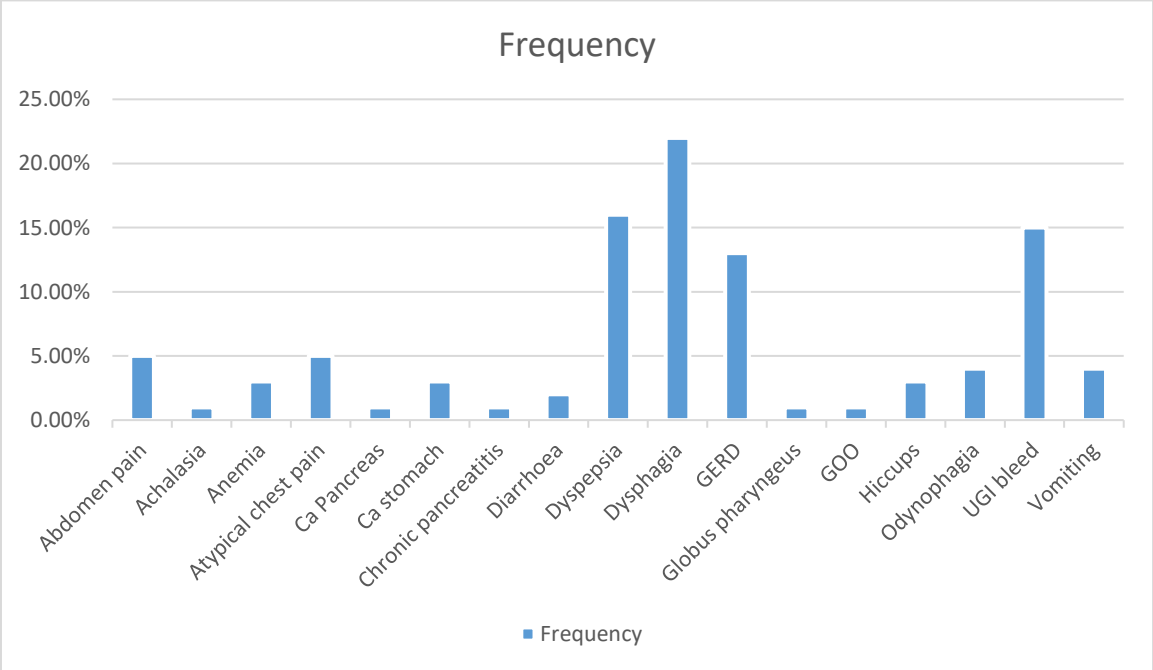

Fig. 4. Various indications for endoscopy in EC cases

4. DISCUSSION

The emergence of esophageal candidiasis (EC) involves a sequential process encompassing esophageal colonization and subsequent penetration of the epithelial layer. This phenomenon is recognized as the initiation of Candida colonization in approximately 20% of healthy adults. Once this colonization is established, compromised immune responses, such as those seen in HIV infections, facilitate the invasion of the epithelial layer [13]. Certain factors contribute to the susceptibility of EC includes use of proton pump inhibitors, H2-receptor antagonists, and prior vagotomy is linked to an elevated EC risk due to their impact on gastric pH. This modification influences the colonization patterns of microorganisms, including Candida, within the esophagus**.** The disturbance of the normal microbial balance by antibiotics can lead to overgrowth and the colonization of Candida species [14]. Even individuals with functional immune systems can be rendered vulnerable to fungal infections. Corticosteroid administration hampers lymphocyte and granulocyte function, reducing the body's ability to combat infections, including fungal ones.EC may manifest in cases of esophageal obstruction, where stagnation promotes excessive Candida proliferation. However, while these factors contribute to EC development, the exact mechanisms underlying

epithelial layer invasion in otherwise healthy individuals remain incompletely understood. In essence, the progression of EC is a multifaceted process, influenced by host-related factors, interactions among microorganisms, and immune responses [15]. Grasping these intricacies is pivotal in devising effective strategies to manage and treat EC in individuals at risk or afflicted by this condition.

Our study is the first attempt to evaluate clinical symptoms, comorbidities, precipitating factors, endoscopic manifestations of candida esophagitis, fungal culture and drug sensitivity in major southern india city Chennai. The main findings of our study was that the prevalence of EC was less observed (0.62%, 100/16000) comparing with the data reported other countries by Underwood, et al. (0.71%, 18/2527) and by Naito, et al.13 (1.17%, 41/3501). We found that one fourth (26%) of our cases were presented with dysphagia followed by nausea (15%), dyspepsia(15%), asymptomatic(11%), regurgitation(9%),chest discomfort (8%),vomiting (6%),odynophagia (5%) and hiccups (5%). We also found that no comorbidities in one fifth of cases (20%) followed by liver disease (17%), malignancy(13%), diabetes(10%), COPD(9%) and HIV(8%).We also found that no precipitating factor in 42% cases of EC followed by PPI/H2RA (23%), antibiotics (13%),immunosuppressants (13%), and inhaled steroids(9%).Certain factors such as older age,male gender, severe anemia, uncontrolled diabetes, a high neutrophil-to-lymphocyte ratio (NLR), and a high ECOG performance status may be associated with an increased risk of fungal infections, including esophageal candidiasis but in our study we didn't idenfied much difference.

In our study we found that more than half(59%) of cases during endoscopy were grade 1 esophageal candidiasis followed by grade 2 EC (32%),grade 3 EC (8%) & oropharyngeal candidiasis observed in (1%).More than one third(39%) of cases candida lesions observed in distal esophagus followed by entire esophagus in (27%),mid esophagus in (24%) and upper esophagus in (10%).

In our study we found that KOH mount positive in 56% cases,we also observed that more than 2/3rd(67%) of EC were due to candida albicans species & one fifth(20%) showed resistance to fluconazole.

The limitations of our study included a small number of patients and no correlation (no consideration) of alcohol consumption or smoking with EC to our study because both of them have influence on EC.

Table 2. Severity grading and extent of candidiasis

		Frequency	Percentage
Grade of candidiasis	1	56	56.0%
	2	32	32.0%
	3	8	8.0%
	4	2	2.0%
	5	1	1.0%
	6	1	1.0%
Site & extent	Upper esophagus	10	10.0%
	Mid esophagus	24	24.0%
	Distal esophagus	39	39.0%
	Pan esophagus	27	27.0%

Table 3. Hb, NLR and RBS Values of EC cases

		Frequency	Percentage
Hb	<11	26	26.0%
	>11	74	74.0%
RBS	<125	47	47.0%
	>125	53	53.0%
NLR	<2	44	44.0%
	>2	56	56.0%

Table 4. ECOG performance, KOH mount status, fungal culture and fluconazole sensitivity of EC cases

		Frequency	Percentage
ECOG performance	0	81	81.0%
	1	19	19.0%
	2	0	0.0%
	3	0	0.0%
KOH mount	Negative	44	44.0%
	Positive	56	56.0%
Fungal culture	Candida albicans	67	67.0%
	Candida non albicans	33	33.0%
Sensitive	Flu,Vor,itr,AmpB	80	80.0%
	Vor,Itr,AmpB	20	20.0%
Resistance for fluconazole	Yes	20	20.0%
	No	80	80.0%

Image 1. Candida albicans culture

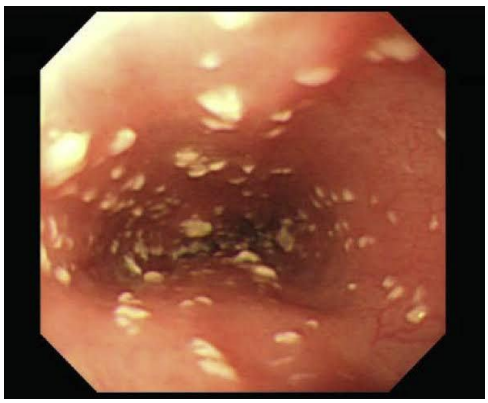

Image 2. Esophageal candidiasis

5. CONCLUSION

In conclusion, Candida esophagitis may be more common than previously suspected. Neither the presenting symptoms nor the endoscopy findings are always classic for this disease. Although the majority of patients included in our study did not have an underlying malignancy or known immunosuppression, multiple predisposing risk factors were noted. All patients were found to have at least one predisposing condition or history of medication use, acid-suppressive therapy being the most frequently noted. Large-size prospective studies are needed to further identify the clinical & microbiological profile of esophageal candidiasis.

CONSENT

Informed consent was obtained from all individual participants included in the study. Patients signed informed consent regarding publishing their data.

ETHICAL APPROVAL

The study was approved by institutional ethics committee

ACKNOWLEDGEMENTS

Availability of data and material: Yes, on request. Ethics approval: The study was approved by institutional ethics committee (No. 29122021). Consent to participate: Informed consent was obtained from all individual participants included in the study. Consent to publish: Patients signed informed consent regarding publishing their data.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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