

Review Article:

## Candida-associated Gastric Ulcer until Yesterday, Today, and from Tomorrow --- In Quest of the Etiology ---

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### Abstract

Candida-associated gastric ulcer, though formerly thought to affect only debilitated persons, has been reported to occur in apparently healthy individuals. Though had been reported to demonstrate nothing but nonspecific endoscopic features, the disease occasionally exhibits an apparently typical finding designated a candidarium. The natural history of the disease had been unknown but the ulcer is shown to not only occur but also recur in a different site with a different shape in a non-diabetic, *Helicobacter pylori* (*H. pylori*)-negative patient without antecedent ulcers or history of the lesions, who has not been given non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics, or antineoplastic agents, which implies that Candida is no innocuous bystander but an etiologic perpetrator. Immune deficiency has recently been reported in relation to candidiasis, which is considered to explain the cause of intractable or recurrent Candida-associated gastric ulcer. In the oropharyngeal field, *Candida albicans* has recently been shown to secrete a hitherto unknown cytolytic peptide pore-forming toxin (PFT), candidalysin, into a pocket in the epithelium which penetrates into and to activate mitogen-activated protein kinase (MAPK)/MAPK phosphatase 1 (MKP1)/c-Fos pathway, triggering release of damage as well as immune cytokines. While the PFT, exerting an effect even on the adjacent cells, directly injures the tissue with damage cytokines, immune counterpart activates polymorphonuclear leukocytes (PMN) to eventually terminate inflammation, which results in restoring the fungus to the commensal state or eradicating it. Since it cannot be negated that such a phenomenon occurs in the gastric mucosa, a theoretically strong possibility has come up that the so-called Candida-associated gastric ulcer is actually Candida-induced ulcer. Therefore, the disease should be reinvestigated in the light of the recent immunological, microbiological, and molecular biological findings.

**Keywords:** Candidarium; Candida-associated gastric ulcer; Candida-induced gastric ulcer; Gastric candidiasis; *Helicobacter pylori*-negative gastric ulcer; Non-NSAID gastric ulcer; Recurrent gastric ulcer

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## Introduction

Though a commensal colonizer ubiquitously detected in the normal human oropharynx to gastrointestinal tract throughout<sup>1</sup>, *Candida* causes infections in the tract under certain conditions, which are more widespread than previously recognized<sup>2,3</sup>. The most frequently involved organ is the esophagus followed by the stomach<sup>2</sup>. Gastric candidiasis is classified into thrush, nodular, and ulcerated type<sup>4</sup>. Though usually seen in immunocompromised hosts<sup>2,3</sup>, the third type, *Candida*-associated gastric ulcer, also occurs in apparently healthy individuals<sup>5,9</sup> with very widely different frequency contingent on the authors<sup>8,12</sup>. The natural history of the disease had not been clarified and the clinical significance of the fungus remains to be elucidated<sup>2</sup> so that the treatment has not yet been established. The fungus had been reported to be no longer detected once the ulcers were healed and no recurrence of the disease had been described<sup>9,11</sup>. The author<sup>13</sup>, however, reported a case of the disease relapsing in a different site with a different shape in an *H. pylori*-negative, non-diabetic patient with no antecedent peptic ulcers or history of the lesions, who had not taken NSAIDs, antibiotics, or antineoplastic agents, speculating that *Candida* plays an etiologic role. This review revisits the disease to investigate the appropriateness of the speculation in the light of the recent microbiological, molecular biological, and immunological findings.

### **Candida Infection of the Gastrointestinal Tract**

*Candida* is totally lacking a life style outside the human body and establishes a colony in the human oropharynx and gastrointestinal and vaginal tracts. Langenbeck<sup>14</sup> is credited with having discovered *Candida* in the cadaveric intestine in 1839 and now *Candida albicans* is proven to be the most frequent commensal fungus in the oropharynx to gastrointestinal tract of the normal human adults<sup>1</sup>. It

increases both in frequency and concentration directed toward the anus: it was detected in 27% of the oropharynx samples obtained by swabbing, 43% of the jejunal and 50% of the ileal aspirates, and 59% of the fecal specimens<sup>1</sup>.

No fungal growth, whether it is *Candida* or not, was detected in the gastric juice with pH value lower than 4.0 and the positive rate of fungal recovery was significantly increased with the elevation of the acidity of the juice<sup>15</sup>. Colonization of *Candida* in the stomach was observed more frequently in older patients<sup>11</sup> and in patients with hypoacidity<sup>16</sup>.

*Candida* is also demonstrated to be the most common fungus causing significant, histologically proven gastrointestinal infection in the debilitated patients: the infection was detected in 13% of the patients with myeloproliferative diseases and in 1.5% of those with solid tumors, respectively<sup>2</sup>. It involved all segments of the gastrointestinal tract but the most frequently afflicted organ was the esophagus followed by the stomach<sup>2</sup>.

*Candida* infection is more widespread than previously recognized<sup>2,3</sup>, shown to occur not only in debilitated but also apparently healthy individuals<sup>3</sup>. Gastric candidiasis is shown to affect 0.96% of all patients undergoing endoscopy and to be more common in men and the elderly<sup>4</sup>. Minoli et al.<sup>4</sup> endoscopically classified the disease into 3 forms: thrush, nodular, and ulcerated, each accounting for 42%, 31%, and 27%, respectively. The first type presents itself as a white or green-white, readily removable membrane of variable extension spreading over the inflamed mucosa in various locations. The second is described as nodular projections of a few millimeters in diameter overlaid by the remarkably inflamed mucosa, mainly located in the antrum. The third has no particular endoscopic features distinct from other peptic ulcers.

### **Candida-associated Gastric Ulcer until Yesterday**

Candida-associated gastric ulcer is regarded as the above mentioned ulcerated-typed gastric candidiasis, the diagnostic criterion of which is demonstration of infiltration of the tissue or ulcer slough by the hyphae<sup>5,8,10</sup>. It is also seen in apparently healthy individuals<sup>5,9</sup> with quite widely different frequency according to the authors<sup>8-12</sup> ranging from 0.12% to 36% of gastric ulcer. The species among the genus reported to be associated with gastric ulcer are albicans, tropicalis, parapsilosis, krusei, and pseudotropicalis in decreasing order of frequency<sup>10</sup>. The natural history of the disease had remained to be clarified<sup>2</sup> and the disease has been reported to engender no specific symptoms<sup>8</sup>. As Minoli et al.<sup>4</sup> described, the endoscopic features of the disease had been asserted to be nonspecific<sup>9,11</sup>.

Whereas some cases have been reported to have spontaneously healed<sup>12</sup>, it has been reported to have low healing rate<sup>6,11</sup>. The rate of decrease in ulcer diameter, an indication of ulcer healing, was slower in patients whose stomachs were significantly colonized by Candida as compared with patients who were not<sup>17</sup>. Brozowski et al.<sup>18</sup> demonstrated that persistent colonization with Candida in the stomach of rats suffering from ulcer induced by acetic acid, which were inoculated with the fungus, was achieved in those treated with antiseptory agents or NSAIDs and that such candidiasis reduces gastric acid secretion, while delaying ulcer healing possibly due to the impairment in the gastric blood flow in the ulcer area and enhanced expression and release of IL-1 $\beta$  and TNF $\alpha$ . Reviewing Crohn's disease, ulcerative colitis, and gastric and duodenal ulcers, Kumamoto<sup>19</sup> points out that significant colonization with Candida is associated with more severe disease and the colonization delays healing of inflammatory lesions and inflammation promotes colonization, producing a vicious circle.

The fungus had been reported to be no longer

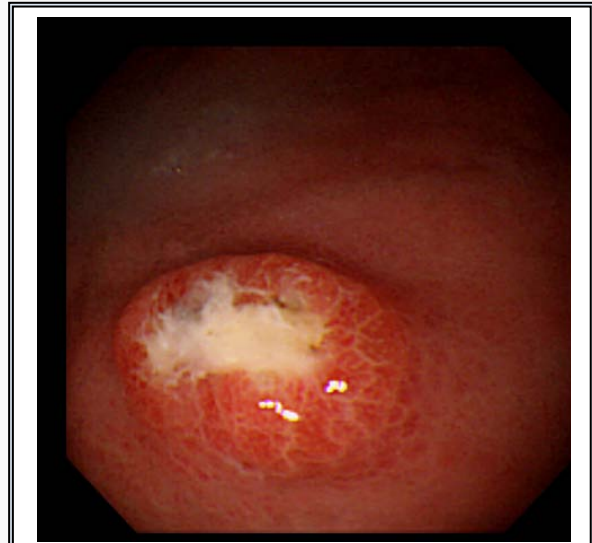
detected once the ulcers were healed even without antifungal treatment and no recurrence had been described<sup>9,11</sup>. Though the clinical significance of the fungus has not yet been elucidated, --- so that the appellation of the disease is modified by an ambiguous adjectival past participle "associated"--- Candida was not regarded as directly etiologic in development of ulcer but was considered to possibly aggravate or perpetuate ulceration<sup>5,6,8</sup>.

The author designates such a state of the recognition of the disease Candida-associated Gastric ulcer until yesterday after one of Dr Jared Diamond's masterpieces. The proofs that Candida exacerbates gastric ulcer or delays its healing are considered to be the proofs that the fungus has the ability to damage the gastric tissues but they by no means deny that it initiates peptic ulcers. No direct evidences, however, have been obtained so far that Candida is ulcerogenic.

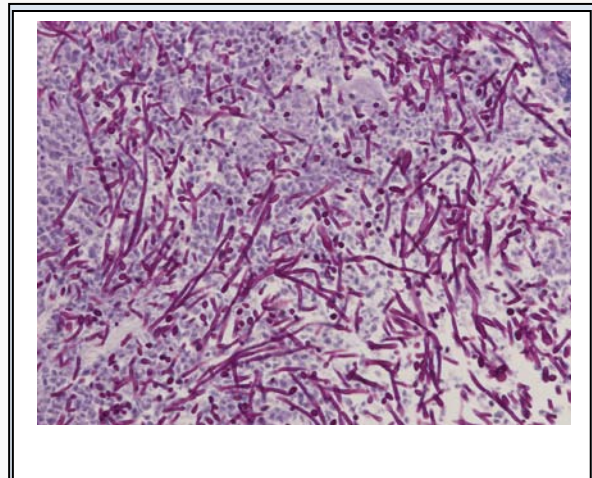
#### **Candida-associated Gastric Ulcer Today**

The author<sup>13</sup>, however, presented a then unreported case of Candida-associated Gastric ulcer in a non-diabetic, *H. pylori*-negative patient with no antecedent peptic ulcers or history of the lesions who had not taken NSAIDs, antibiotics, or antineoplastic agents. The first ulcer was detected in an 87-year-old, Japanese housewife complaining of anorexia as a medium-sized, submucosal tumor (SMT)-like elevation overlaid with the erythematous mucosa with an oval, deep, central ulceration covered with thick whitish exudate designated a candidarium (*vide infra*) on the greater curvature of the upper gastric body (Figure 1). No signs of candidiasis were detected in the oropharynx through esophagus or in the duodenal bulb through descending part of the duodenum. She had endoscopically been shown to have no such lesions or scars in the upper or no signs of candidiasis in the lower gastrointestinal tract 2 months before. She had no past history of peptic ulcers. Biopsy showed no

malignancy or *H. pylori* but countless hyphae in the ulcer slough (Figure 2), which were proven to be *Candida* (*C.*) *tropicalis* by culture. She, though diagnosed as having *Candida*-associated gastric ulcer, refused to be treated.

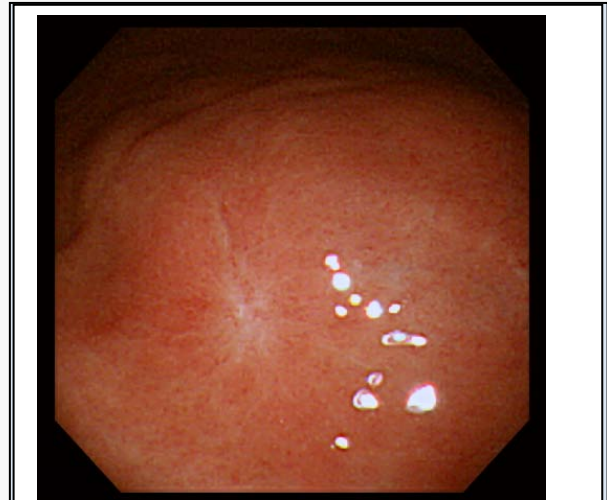


**Figure 1:** Endoscopic photograph showing a medium-sized, SMT-like elevation with an oval, deep, central ulceration covered with thick, whitish exudate designated a candidarium (see text) on the greater curvature of the upper gastric body.



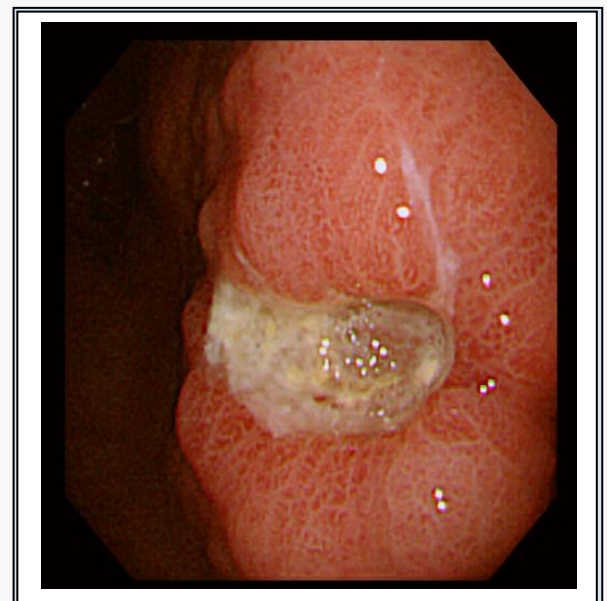
**Figure 2:** Light micrograph of the biopsied specimen from the candidarium in Figure 1 demonstrating innumerable hyphae in the ulcer slough (PAS/diastase, original magnification x400).

The lesion was shown to have spontaneously turned into a white scar (Figure 3) 10 months later, when she



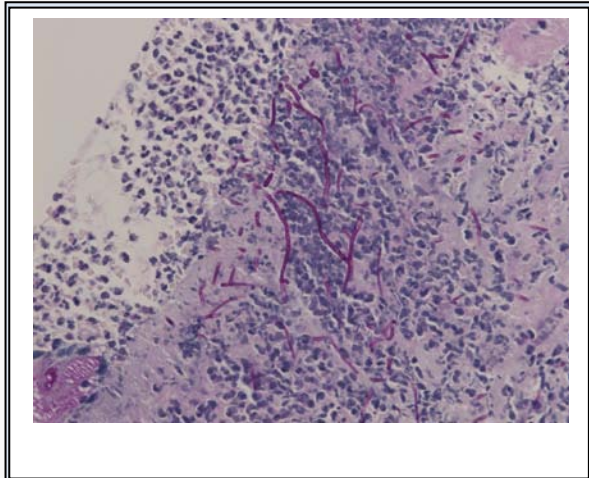
**Figure 3:** Endoscopic photograph showing the white scar of the original ulcer.

complained of heartburn, but another large, oval, deep ulcer was detected covered with thick, whitish exudate surrounded by the markedly swollen margin on the lesser curvature of the lower gastric body



**Figure 4:** Endoscopic photograph showing a recurrent ulcer on the lesser curvature of the lower gastric body.

(Figure 4). Biopsy demonstrated numerous hyphae again (Figure 5). *H. pylori* was not detected by



**Figure 5:** Light micrograph of the biopsied specimen from the recurrent ulcer demonstrating numerous hyphae of *Candida* in the ulcer edge. (PAS/diastase, original magnification x400).

histologic examination or rapid urease test. No findings of candidiasis were recognized in the oropharynx through other parts of the upper gastrointestinal tract. She was diagnosed with *Candida*-associated gastric ulcer recurrent in a different location with a different appearance. The lesion was proven to have turned into a red scar (Figure 6) in 6 weeks with administration of a proton pump inhibitor (PPI) without an antifungal agent and into a white in 3 months (Figure 7)<sup>13</sup>.

While endoscopic features of *Candida*-associated gastric ulcer had been asserted to be nonspecific<sup>4,9,11</sup> an SMT-like lesion with a deep, central ulceration has been regarded as specific by some Japanese authors<sup>20,21</sup>. In the author's case, the original lesion did indeed assume such a form (candidarium)<sup>13</sup>. Since such an appearance has been detected only in Japanese patients<sup>20,21</sup>, it might be peculiar to the race and is considered suggestive of *Candida*-associated gastric ulcer. The author proposes to designate the lesion a candidarium (*Candida* hill; *Candida*, the genus of the fungus, originally a Latin feminine adjective meaning bright + *arium*, a Latin neutral substantive-forming suffix usually denoting a place) after a formicarium

(anthill; *formica*, a Latin feminine noun signifying an ant). Whereas the disease has been reported to have



**Figure 6:** Endoscopic photograph showing the red scar of the recurrent ulcer.



**Figure 7:** Endoscopic photograph showing transition from the red to white scar in 3 months.

low healing rate<sup>6,11</sup>, some cases of the disease have been reported to have spontaneously healed<sup>12</sup>. In the author's case, the original lesion was found to have spontaneously healed and the recurrent one was in no way intractable<sup>13</sup>. The intractability of the disease may be affected by other factors than the fungus per se, such as *H. pylori*, NSAIDs, or specifically impaired

immune response of a host to the fungus because such factors were not inspected in the cases reported to be intractable<sup>6,11</sup>.

Candida had been reported no longer detected once the ulcers were healed<sup>9,11</sup> and the natural history of Candida-associated Gastric ulcer had still been to be elucidated<sup>2</sup>. The author's case<sup>13</sup>, however, is the first in the world, which was demonstrated to have recurred not only in a different site but with a different appearance and followed up from before development of the original ulcer till complete cicatrization of the recurrent, disclosing the natural history of the disease: the fungus is not considered an innocent bystander, which is secondarily detected in an already existing ulcer.

### **Candida-associated Gastric Ulcer from Tomorrow**

#### **1. Is Candida-associated Gastric Ulcer Candida-induced Ulcer?**

Detected both in the original and recurrent lesions in an *H. pylori*-negative patient with no antecedent ulcers who had not taken NSAIDs, antibiotics, or antineoplastic agents, Candida was considered, contrary to the prevailing opinion, to play an etiologic role in ulcer formation<sup>13</sup>. The author speculated that the fungus exerted the direct gastric mucosal damage in the setting of the compromised mucosal defense in the elderly patient. Such a tissue injury could be aggravated by the presence of gastric acid, however weakened by old age. Such a situation is considered to result in ulcer, in the slough of which numerous hyphae are detected.

The author infers as follows. This is not simply only one case of Candida-associated gastric ulcer but is, as it were, the only one fossil luckily unearthed in its integrity. Though dug out, other fossils are marred by *H. pylori*, NSAIDs, antibiotics, antineoplastic agents, and so on in the extremely specific environment, the stomach, in which peptic ulcer occurs not rarely from

different causes, so that they leave so much to be desired to reflect the whole picture of the bona fide Candida-associated gastric ulcer. This is not a peculiar one or exception, which is incidentally discovered by a whimsical endoscopist but the theoretically predictable missing link, which connects Candida-associated gastric ulcer in the dark age to Candida-induced gastric ulcer in the era enlightened by the splendid future researchers. It is an ideal model, which represents all the natural gastric ulcers associated with Candida infection and is never excavated frequently.

It is the ability of Candida to switch from the yeast to hyphal form, by which the different genes of the fungus are expressed, that is crucial in causing pathogenicity at the mucosal surfaces<sup>22</sup>. Wächtler et al.<sup>23</sup> demonstrated that *C. albicans* hyphae can invade TR-146 epithelial cells through two distinct mechanisms, induced endocytosis and active penetration, and that the latter is the dominant invasion route. Jacobson et al.<sup>22</sup> showed that it is only the active penetration of the hyphae which causes epithelial damage. Silva et al.<sup>24</sup> demonstrated that *C. tropicalis* filaments are highly invasive with the ability to induce tissue damage in a reconstituted human oral epithelium (RHOE) system with no involvement of aspartyl proteinases (SAPs), the key hydrolytic enzymes secreted by the fungus, implying the existence of a still unknown mechanism.

Moyes et al.<sup>25</sup> demonstrated that oral epithelial cells, discriminating between the yeast and hyphal forms of *C. albicans*, exhibited a biphasic MAPK response. The first phase of the response is provoked when fungal burdens are light, which constitutes weak activation of all MAPK pathways, p38, c-Jun N-terminal kinase (JNK), and extracellular signal-regulated protein kinases 1 and 2 (ERK1/2) together with nuclear factor kappa-light-chain-enhancer of activated B cells (NF- $\kappa$ B) independent of the fungus

morphology. This results in activation of the transcription factors NF- $\kappa$ B and c-Jun through ERK1/2 and JNK, which is not strong enough to induce immune activation, allowing the fungus to remain in the commensal state. The second phase is observed when fungal burdens are heavy, which is dependent upon hypha formation, constituting activation of the transcription factor c-Fos through p38. In addition, the hyphae activate MKP1 through ERK1/2 pathway, which acts to regulate p38 and JNK signaling. MAPK/MKP1/c-Fos activation results in immune activation and secretion of proinflammatory cytokines. Such events ultimately lead to PMN recruitment and fungal clearance or burden reduction, namely a return to the commensal state<sup>26</sup>.

Moyes et al.<sup>27</sup> have recently succeeded in clarifying how *Candida albicans* induces epithelial inflammatory responses and cell damage during mucosal infections: they identified and characterized the first cytolytic,  $\alpha$ -helix, peptide toxin or PFT isolated from any human fungal pathogen as the hyphal factor critical for epithelial immune activation and mucosal infection of the fungus. The hyphae invade the epithelium to create invasion pockets, into which they secrete the toxin Ece1-III designated “candidalysin” by Moyes et al.<sup>27</sup>, thereby triggering the above mentioned second phase of MAPK response, which issues in production of immune regulatory cytokines, such as IL-6, G-CSF, and GM-CSF, at the sublytic concentrations. As the toxin increases in amount to reach the lytic concentration, it damages the epithelium to release damage cytokines, such as IL-1 $\alpha$ . Candidalysin, if produced sufficiently, appears to exert an effect on the epithelial surface outside of the invasion pocket as well as on the adjacent cells not in contact with the hyphae<sup>27</sup>. A logically definitive possibility has opened up that *Candida*-associated gastric ulcer is provoked by

the direct action of the fungus so that the disease should be designated *Candida*-induced ulcer instead of *Candida*-associated.

## **2. Is the PFT-MAPK/MKP1/c-Fos System Applicable to *Candida*-associated Gastric Ulcer?**

Candidalysin-MAPK/MKP1/c-Fos system was established only in regard to *Candida albicans* in vitro TR146 buccal epithelial squamous cell carcinoma line system and in vivo with the use of female Balb/c mice oropharyngeal candidiasis model modified for investigation of early infection events<sup>27</sup>. Does what occur in the squamous epithelium also occur in the gastric mucosa?

Lee et al.<sup>28</sup> demonstrated that *C. albicans* pre-vacuolar protein sorting gene VPS4 is required for extracellular secretion of the secreted aspartyl proteases Sap2p and Saps4-6p and that the *C. albicans* vps4 $\Delta$  null mutant is markedly hypovirulent in a standard murine tail vein model of disseminated candidiasis<sup>29</sup>. Thereafter their group<sup>30</sup> explored the role of the pre-vacuolar secretion pathway mediated by VPS4 in the pathogenesis of epithelial and mucosal infection using a wide range of virulence models, obtaining the results which suggest that VPS4 contributes to several key aspects of oral epithelial but not uroepithelial infection and no major part in the pathogenesis of *Candida* vaginitis in contrast to disseminated candidiasis. They<sup>30</sup> concluded that *C. albicans* VPS4 contributes to virulence according to the specific tissue that is infected.

Vautier et al.<sup>31</sup> performed the following experiments in order to examine which morphology of *C. albicans* best fits to colonize the organs of the GI tract by analyzing respective fungal burdens at various organs. Mice, which were pretreated with oral administration of antibiotics to reduce the commensal bacterial and fungal microbiota, were perorally infected with wild-type strains (SC5314 and CAI4) as well as strains carrying mutations locking them into the yeast

(*efg1Δ/cph1Δ*) or filamentous forms (*nrg1Δ*). Animals infected with the filamentous-locked strain showed lower burdens in the small intestine, cecum, and large intestine, whereas those infected with the yeast-locked strains had similar or higher burdens as compared with those infected with wild types. Those infected with the filamentous-locked strain of MBY38 demonstrated significantly lower tissue fungal burdens, as well. Colonization in the murine intestinal tract was, therefore, shown to favor the yeast form of *C. albicans*. Whereas in the stomach, both the strains locked into the yeast and into the hyphal form were recovered at lower levels as compared with the wild-type strains. These results suggest that it is essential that the fungus be provided with the ability to shuttle between both the morphologies in order to colonize in this specific organ. Correlated with their reduced fungal burden in the stomach, decreased levels of cytokines, IL-1 $\beta$ , IL-6, and IL-17, which are involved in mediating Th17 responses<sup>32</sup>, were detected in the organ of the mice infected with both yeast- and filamentous-locked *C. albicans* strains. Such phenomena were not observed in any other organs<sup>31</sup>. These results endorse preferential infection of the stomach in the experimental model<sup>32</sup> and the fact that the colonization is restricted to the lumen elsewhere in the GI tract<sup>31</sup>.

Though Th17 immunity is required for controlling *C. albicans* infections at the mucosa, the significance of decreased level of these cytokines produced by both the yeast- and filamentous-locked strains colonizing in the stomach remains to be elucidated. No experiments were conducted concerning the possibility that interfering with Th17 responses would influence colonization of the fungus restricted to the organ by blocking the effects of IL-1 $\beta$  or IL-17.

Though, reflecting the organ-specificity in *C. albicans* infection in the experimental animal models described

above, the predominant morphology of wild-type *Candida*, which has the ability to shuttle from yeast to hyphal form, differs from infected organ to organ<sup>18</sup>, the fungus shows hyphal form in *Candida*-associated gastric ulcer<sup>4,6,8,10,12,13,20</sup>. If the fungus can transgress the mucus barrier of the stomach and overcome the inhibitory action of the serum<sup>20</sup> and if candidalysin is not inactivated by gastric acid, at least in an invasion pocket, *Candida* is thought to be able to penetrate actively into the gastric mucosa to provoke ulcer by the PFT and damage cytokines produced by MAPK/MKP1/c-Fos pathway<sup>27</sup> with the aid of gastric acid. Though such a phenomenon has not been confirmed in human *C. albicans*-associated gastric ulcer, it does not appear irrational to infer so. Differences exist in how the hyphae activate the pathway in the epithelial cells of the different organs, a common mechanism, which enables different epithelial tissues to orchestrate innate immune response specifically against them<sup>34</sup>, however.

But does such an event occur only in a case of *C. albicans*-associated gastric ulcer and not in a case of non-*C. albicans* *Candidae* (NCACs)? Moyes et al.<sup>35</sup> demonstrated that no NCACs exhibit true hyphal forms but *C. dublinensis* in vitro. Though Silva et al.<sup>24</sup> reported that *C. tropicalis* was highly invasive with the ability to induce significant tissue damage, exhibiting the filament formation, in the same in vitro system ( $2 \times 10^6$  fungus cells onto TR146 cell line), as Moyes et al.<sup>35</sup> used. The latter<sup>35</sup> claimed that invasion and cytokine production by *C. tropicalis* was significantly lower than that induced by *C. albicans* in their experimental system and that, albeit *C. tropicalis* may form “hyphal-like” structures in vivo to activate epithelial cells, it is unlikely that they will parallel the true hyphae produced by *C. albicans* et *dublinensis* and are thus unlikely to possess the same hyphal moiety shared by *C. albicans* to activate the epithelial



cells via MAPK/MKP1/c-Fos pathway.

The author<sup>13</sup> presented a case of *C. tropicalis*-associated gastric ulcer, in whose slough innumerable obvious hyphae were detected, as in a case of *C. albicans*-associated gastric ulcer<sup>12</sup>. The similar phenomenon provoked by candidalysin is considered to be generated not only in *C. albicans*- but also in NCAC-associated gastric ulcer. Since the PFT-MAPK/MKP-1/c-Fos system, though there exist various PFTs, are generally recognized in the wide variety of bacterial infections<sup>36</sup>, it is unlikely that *C. albicans* is the sole species which possesses PFT among the genus. It is not at all difficult to deduce that fastidiousness of *C. tropicalis* renders the obvious hypha formation irreproducible in vitro and that, therefore, the true in vivo events engendered by the fastidious fungus has by no means been able to be investigated in vitro until now. Establishment is expected of the proper in vitro experimental system of NCACs.

### 3. Adaptive Immunity against *Candida*

Weindl et al.<sup>36</sup> stated that the adaptive immune system established by the MAPK/MKP1/c-Fos pathway expels *C. albicans* which has invaded. Such a finding warrants the fact that *Candida*-associated gastric ulcer is treatable by a PPI without antifungal agents<sup>9,11</sup>. Then, the recurrence of the gastric ulcer reported by the author<sup>13</sup> is considered to be due to the antigenic shift of the fungus or due to impaired immune response of the host.

Th17 cells secrete interleukins IL-17A and IL-17F, which stimulate a variety of cells to produce antimicrobial peptides and chemokines promoting neutrophil recruitment and activation<sup>37</sup>. Patients with defects affecting segments of innate and acquired immunity which disrupt the Th17 pathway are reported to be unable to clear superficial *Candida* infections and to develop chronic mucocutaneous

candidiasis<sup>38</sup>. von Bernuth et al.<sup>39</sup> stated that, though humans with inborn MYD88 or IRAK-4 deficiency suffer from a few naturally occurring life-threatening bacterial infections, toll-like receptor (TLR)- and IL-1R-dependent immunity mediated by such genes is crucial only in infancy and early childhood in the natural setting in contrast to the murine counterpart. But Vogelaar et al.<sup>40</sup> reported a case of a young adult with recurrent candidiasis, who had a germline homozygous missense variant in MYD88 and exhibited a defective production of IL-17 upon stimulation with *Candida albicans*.

The defects in Th17-IL-17 system are considered to be involved in the cause of intractable and/or recurrent *Candida*-associated gastric ulcer.

### Closing Remarks

Owing to the recent advances in microbiology, molecular biology, and immunology, a logically definitive possibility has emerged that the so-called *Candida*-associated gastric ulcer is *Candida*-induced ulcer. The disease has come to a stage, in which the etiology should be reinvestigated and the disease itself should be reconsidered in the light of not only pathogens' character but also hosts' immunological status.

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The author declares that he has no conflict of interests concerning this article.

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